VOLUME 52 NUMBER 3 MARCH 1959

PROCEEDINGS
of the
ROYAL
SOCIETY OF MEDICINE

Published by
THE ROYAL SOCIETY OF MEDICINE, 1 WIMPOLE STREET, LONDON, W.1

the better for

Benadryl is a reliable and potent histamine antagonist for symptomatic control of hay fever and many other allergic disorders . . .
Benadryl is especially effective in urticaria and other pruritic conditions of allergic ætiology in relieving food and drug sensitivities and, as an antispasmodic, in alleviating such conditions as spastic colitis and nocturnal leg cramps.
Benadryl capsules provide easy and practical dosage for adults and older children. Benadryl Elixir is palatable and well-tolerated by infants. Products of Benadryl for parenteral and topical use are also available.

BENADRYL*

ANTIALLERGIC
ANTISPASMODIC

*Trade Mark

BENADRYL* (Diphenhydramine hydrochloride, B.P.C., Parke-Davis) is supplied in capsules of 25 mg. and 50 mg. or as BENADRYL ELIXIR containing 10 mg. in each teaspoonful.

PARKE, DAVIS & CO. LTD. (*Inc. U.S.A.*) HOUNSLOW, MIDDLESEX. TEL: HOUNSLOW 2361.

WPS. 1005

VOLUME 52 NUMBER 3 MARCH 1959

PROCEEDINGS

of the

ROYAL SOCIETY OF MEDICINE

All correspondence to
THE HONORARY EDITORS, 1, WIMPOLE STREET, LONDON, W.1
(Tel.: LANgham 2070)

Distributing Agents:
H. K. LEWIS & CO. LTD., 136 GOWER STREET LONDON, W.C.1

In the U.S.A.:
GRUNE & STRATTON, INC., 381 FOURTH AVENUE, NEW YORK 16

Advertisement Managers:
H. S. JANES & PARTNERS LTD., 99 GOWER STREET, LONDON, W.C.1
Telephone: EUSton 3221

Monthly, 10s. 6d. net. Annual Subscription, £6 6s. in the British Commonwealth, $19.00 in the U.S.A.

the better for

Benadryl is a reliable and potent histamine antagonist for symptomatic control of hay fever and many other allergic disorders . . .
Benadryl is especially effective in urticaria and other pruritic conditions of allergic ætiology in relieving food and drug sensitivities and, as an antispasmodic, in alleviating such conditions as spastic colitis and nocturnal leg cramps.
Benadryl capsules provide easy and practical dosage for adults and older children. Benadryl Elixir is palatable and well-tolerated by infants. Products of Benadryl for parenteral and topical use are also available.

BENADRYL*

ANTIALLERGIC
ANTISPASMODIC

*Trade Mark

BENADRYL* (Diphenhydramine hydrochloride, B.P.C., Parke-Davis) is supplied in capsules of 25 mg. and 50 mg. or as BENADRYL ELIXIR containing 10 mg. in each teaspoonful.

PARKE, DAVIS & CO. LTD. (*Inc. U.S.A.*) HOUNSLOW, MIDDLESEX. TEL: HOUNSLOW 2361.

WPS. 1005

VOLUME 52 NUMBER 3 MARCH 1959

PROCEEDINGS

of the

ROYAL SOCIETY OF MEDICINE

All correspondence to
THE HONORARY EDITORS, 1, WIMPOLE STREET, LONDON, W.1
(Tel.: LANgham 2070)

Distributing Agents:
H. K. LEWIS & CO. LTD., 136 GOWER STREET LONDON, W.C.1

In the U.S.A.:
GRUNE & STRATTON, INC., 381 FOURTH AVENUE, NEW YORK 16

Advertisement Managers:
H. S. JANES & PARTNERS LTD., 99 GOWER STREET, LONDON, W.C.1
Telephone: EUSton 3221

Monthly, 10s. 6d. net. Annual Subscription, £6 6s. in the British Commonwealth, $19.00 in the U.S.A.

PROCEEDINGS
of the
ROYAL SOCIETY OF MEDICINE

Vol. 52 No. 3 March 1959

CONTENTS

Continued overleaf

CONTENTS (*continued*)

N.B.—The Society does not hold itself in any way responsible for the statements made or the views put forward in the various papers.

Chelated Iron in Pregnancy and Paediatrics

Two Recent Trials

Plesmet-Ferrous aminocetosulphate complex was shown in two recent clinical trials (1. 2.) to produce impressive results in anaemia of pregnancy and in hypochromic anaemia of children.

In these two trials with PLESMET in 51 pregnant patients and 32 young children with hypochromic anaemia, attention was drawn to the rapid absorption and utilization of iron in this form and to the effective haemoglobin levels attained (an average daily rise of 1%).

Toleration in both groups was excellent and gastrointestinal disturbances were virtually absent.

For treatment or prophylaxis PLESMET provides an ideal form of oral iron at low prescription cost.

Plesmet

Tablets each containing the equivalent of 50 mg. Ferrous Iron with 1 mg. Aneurine Hydrochloride B.P.

Bottles of 100 — 2/8
Bottles of 1000 — 17/6

Basic N.H.S. Price

Syrup each teaspoonful contains: the equivalent of 25 mg. Ferrous Iron with 1 mg. Aneurine Hydrochloride B.P. in a blackcurrant flavoured syrup. (Specially recommended for children, and for adults who cannot take tablets.)

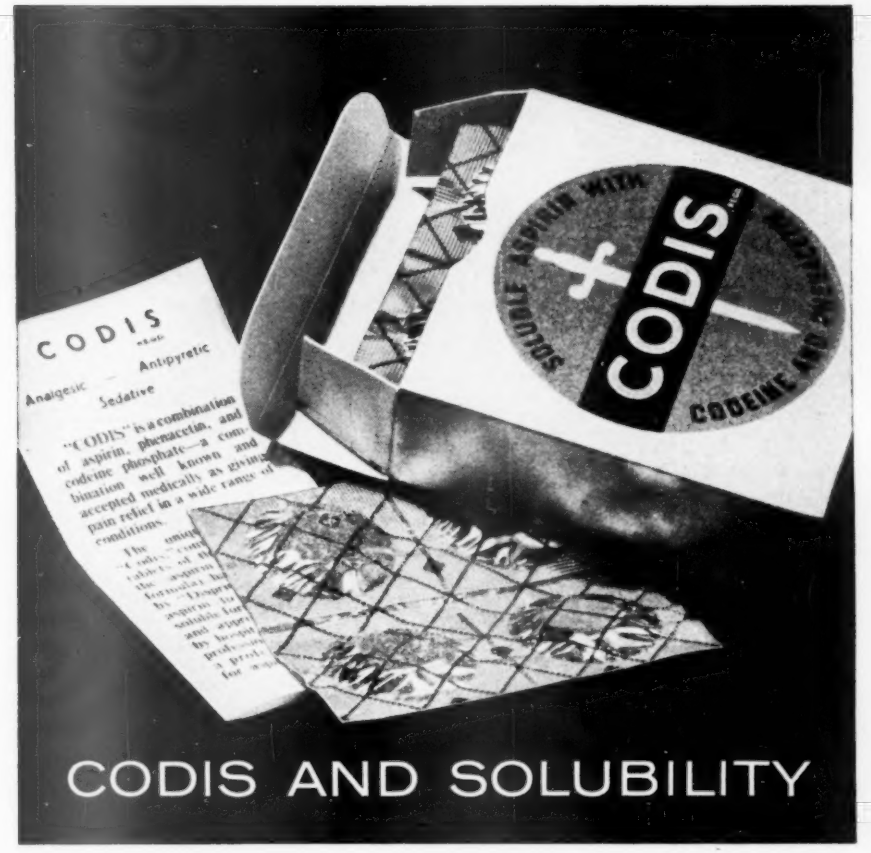
Bottles of 2 oz.—2/-
Bottles of 40 oz.—18/-

References: 1. *Practitioner*, 1958, 181, 731.
2. *Practitioner*, 1958, 181, 736.

C&C LTD. REGD. TRADE MARK

COATES & COOPER LTD.

PYRAMID WORKS • WEST DRAYTON • MIDDLESEX



THE GREAT ADVANTAGE of Codis is that it provides a codeine compound tablet in which the aspirin content is soluble in water. (The codeine constituent is also soluble, and the phenacetin is in very fine suspension.)

This is achieved by careful compounding and preparation, resulting in tablets which are quickly absorbed and well tolerated—even in cases of proven intolerance to ordinary (insoluble) aspirin.

To ensure stability and easy identification, the tablets are wrapped in moisture-proof distinctive gold foils of 10 tablets each (dispensing size), or boxes containing five foils of 4 tablets each (public size).

CODIS REGD. **AVAILABLE FOR DISPENSING**

Not advertised to the public

Composition. *Each Codis tablet contains: Acid. Acetylsalicyl. B.P. 4 gr., Phenacet. B.P. 4 gr., Codein. Phosph. B.P. 0.125 gr., Calc. Carb. B.P. 1.2 gr., Acid. Cit. B.P. (exsic.) 0.4 gr.*

For clinical samples and literature, please write to Reckitt & Sons Ltd., Pharmaceutical Dept., Hull

CONFIDENCE

Delfen

Preceptin

Ortho-Gynol

Ortho-Creme

Ortho

Ortho

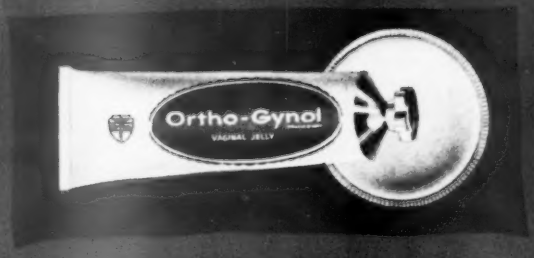
Ortho Pharmaceutical Limited · High Wycombe · England

for

CONFIDENCE

Delfen

Preceptin



Ortho-Gynol

Ortho-Creme

Ortho

Ortho

LITERATURE ON REQUEST

Ortho Pharmaceutical Limited · High Wycombe · England

Section of Physical Medicine

President—KENNETH LLOYD, M.R.C.P.

Meeting November 12, 1958

Some Hazards of Athletic Exercise [*Abridged*]

PRESIDENT'S ADDRESS

By KENNETH LLOYD, M.R.C.P.

Cardiff

THE ancient civilizations realized the importance of maintaining and developing brawn, agility and skill with weapons in their soldiery and young men and so evolved many sports and pastimes designed to develop these physical qualities. For instance, the ancient Greek Olympiad embraced foot races, the broad jump, throwing the javelin and discus, wrestling, chariot racing and a form of boxing. In this country in mediæval times archery, jousting, tossing the pole, throwing the hammer, pole vaulting and various types of sword play were practised to a similar end. In the early nineteenth century the Prussians introduced gymnastics in an attempt to produce an army fit enough to beat the all-conquering Napoleon; about the middle of that century athletic sports began to be encouraged within our own Army and later at our universities. At the end of that century the modern Olympiad was founded and has since served as a spur to the fostering of these ancient sports throughout the world.

In this atomic age the necessity for brawn and agility in the young men of our Forces has practically disappeared and in our daily work it is rapidly disappearing since the advent of mechanization and automation. Brain and skill are taking over and we are becoming increasingly sedentary. However, there appears to be an innate instinct in most of us to use the physical powers with which we have been endowed. Sport is the logical outlet for this instinct and the vast increase, particularly during the past thirty years, in the number of men and women partaking in sports of all kinds is, I believe, the result of this urge. The advent of still shorter working hours giving more leisure is likely to perpetuate this increase and accordingly the demand for playing fields and sports facilities of all types will also increase as will the need for medical men interested in dealing with the resultant injuries.

Many of the ancient sports have undergone considerable modification over the years; these modifications have had two main factors in view, firstly to reduce mortality and morbidity, and secondly to increase the degree of skill called for in the performance of the particular sport. In contrast, most of our ball games and team games are of comparatively recent origin and some of them have not yet undergone sufficient modification to reduce the accident rate, for it is well established that from the Rugby and Association football fields come the majority of serious injuries, some of which result in permanent morbidity. Contributions to this subject were made here in the Society's house two years ago by Fell (1956), who found that Rugby football was the most dangerous game at Cambridge closely followed by Association football, and also by Wynn-Parry (1956), whose experience in the R.A.F. put Association football as the most dangerous as judged by the severer types of traumatic lesions resulting from these games. It is a similar story from America where Thorndike (1956), reporting injuries sustained at Harvard University, found American football and baseball the most dangerous.

Broadly it is those sports involving bodily contact between the players that are the most productive of injury; Rugby and Association football, polo, lacrosse, boxing and wrestling being the chief offenders in approximately that order. Relatively safe sports are regarded as weight-lifting, cycling, athletics, swimming, rowing, fencing, tennis, golf and bowls; none of these involves bodily contact.

The holding of the VI British Empire and Commonwealth games at Cardiff in the summer of 1958 gave me the opportunity to study the types of injury arising from track and field athletics, boxing, wrestling, weight-lifting, swimming, fencing, rowing, cycling and lawn bowls.

The athletes, both male and female, came from thirty-five member countries of the Commonwealth and Empire and were accommodated in a hutted "Village" for approximately one month. The first three weeks of this time were devoted to acclimatization and final training before seven days of competition. Resident at the Village were:

	Men	Women	Total
Athletes	963	159	1,122
Team Officials ..	216	27	243
			1,365

The ratio of men to women was 6 : 1 and two team officials were required to look after every nine athletes, quite apart from the many hundreds of other officials required during competition.

Of this body of 1,122 fit men and women nearly half reported sick because of illness or injury, some for more than one condition. Table I shows that 598 separate diagnoses were made during the four weeks in question, a diagnosis rate of 53%, and that the number of injuries was roughly double that of illnesses. Wrestling proved nearly twice as hazardous as any of the other sports; boxing, the only other contact sport, was, surprisingly slightly less hazardous than athletics but one observed that boxers did not report minor contusions as did competitors from other sports in which they were less common and not regarded as an inevitable hazard. It was also surprising that fencing proved slightly more hazardous than weight-lifting and that rowing and cycling were relatively unproductive of injury.

TABLE I

Sport	Competitors	Injury diagnoses	Illness diagnoses	Total diagnoses
Athletics	424	200 (47·2%)	87 (20·5%)	287 (67·7%)
Boxing	98	44 (44·9%)	28 (28·6%)	72 (73·5%)
Wrestling	59	48 (81·3%)	14 (23·7%)	62 (105·0%)
Weight lifting	67	23 (34·4%)	10 (14·9%)	33 (49·3%)
Swimming and diving	148	36 (24·3%)	35 (23·6%)	71 (48·0%)
Fencing	60	21 (35·0%)	6 (10·0%)	27 (45·0%)
Rowing	101	11 (10·9%)	10 (9·9%)	21 (20·8%)
Cycling	82	8 (9·7%)	13 (15·8%)	21 (25·5%)
Lawn bowls	83	1 (1·2%)	3 (3·6%)	4 (4·8%)
Total	1,122	392 (34·9%)	206 (18·4%)	598 (53·3%)
Team officials	243	4 (1·6%)	28 (11·5%)	32 (13·2%)

If one regards the figures for the team officials as giving an indication of the sickness rate (11·5%) in an average adult population at that time and under the circumstances prevailing then it is apparent that the sickness rate amongst athletes (18·4%) was considerably above average. The injury rates are not comparable but it can be inferred that in two-thirds of the sports the injury rate was unduly high and it is worth noting that only in cycling and lawn bowls was the injury rate lower than the sickness rate.

These high sickness and injury rates I regard as an expression of the fact that to a first-class athlete in peak condition a minor illness or minor injury is a major catastrophe as far as his performance in top-class competition is concerned.

That the majority of these incidents were of a relatively minor nature is reflected in the hospital admissions (Table II), for only 2·3% of injuries required admission.

Of the 206 cases of illness, respiratory infections (42%), gastro-enteritis (20%) and soft tissue infections (12%) predominated, even of the 15% admitted the majority were of such a nature as would normally have been treated in bed at home. In contrast were the team officials' illnesses (10·7%) which comprised coronary thrombosis, heart failure and a vesical calculus. These details are given in order to put the following injury analysis into proper perspective.

TABLE II

	Injury diagnoses	Hospital admissions	Illness diagnoses	Hospital admissions
Athletes	392	9 (2·3%)	206	31 (15·0%)
Team Officials	4	0 (0·0%)	28	3 (10·7%)

The hazards that were encountered have been divided into muscle and tendon tears and strains, joint sprains and traumatic synovitis, and a group of various lesions comprising contusions, lacerations, abrasions, blisters and fractures. In the detailed injury analysis athletics has been subdivided into running, jumping, and throwing as the basic physical actions are different although jumping also involves some running.

Table III shows the distribution of muscle and tendon tears and strains throughout the various sports. Of 171 such lesions the largest group is minor muscle lesions and includes cases of generalized or localized muscle stiffness as well as those of pain apparently arising in muscle but not definitely diagnosable as a strain. The next most frequent occurrence was tears of the hamstring and quadriceps musculature in almost equal numbers, but observe how these lesions are distributed throughout the various sports and the most outstanding feature is that runners tear their hamstrings nearly five times more frequently than their quadriceps, whereas jumpers tear their quadriceps more than twice as often as their hamstrings, but the incidence of calf muscle tears is approximately equal in the two sports. Weight lifters and fencers also produced some quadriceps tears and, as one might expect, the shoulder girdle muscles suffered in wrestling, swimming, fencing and throwing.

Athletics accounted for 63% of all these lesions, the highest incidence being amongst runners (39%) but one must not forget that there were many more competitors at risk in athletics than in any other sport. The absence of severe muscle or tendon strains in rowers and cyclists is noteworthy and this point will be referred to later.

TABLE III.—MUSCLE AND TENDON TEARS AND STRAINS (Percentages in Parentheses)

		Athletics											
		Running	Jumping	Throwing	Boxing	Wrestling	Weight lifting	Swimming and diving	Fencing	Rowing	Cycling	Bowls	Total
LEG	Minor lesions	14 (21)	2	1	2 (33)	2 (14)		6 (37)		6 (86)	2		35 (20)
	Psoas	2					1						3
	Quadriceps	5 (7·5)	12 (41)		1	2	3 (50)	2	4				29 (17)
	Adductors	1	3 (10)						1				5
	Gluteal	2	1						1				4
	Hamstrings	23 (34)	5 (17)	1		2 (14)							31 (18)
	Calf	5 (7·5)	3 (10)	1		1		2					12 (7)
	Tendo achillis	7 (10)	2			1							10 (6)
	Anterior tibials	6 (9)				1		1					8
ARM	Tennis elbow			1					2				3
	Triceps			2 (17)	2 (33)		1						5
	Biceps			2 (17)									2
	Shoulder girdle	1	1	3 (25)	1	5 (36)	1	5 (31)	4 (33)	1			22 (13)
	Teno-synovitis	1		1									2
	Totals	67 (39)	29 (17)	12 (7)	6 (4)	14 (8)	6 (4)	16 (9)	12 (7)	7 (4)	2 (1)	0	171 (100)

TABLE IV.—SPRAINED JOINTS AND TRAUMATIC SYNOVITIS (Percentages in Parentheses)

	Athletics											
	Running	Jumping	Throwing	Boxing	Wrestling	Weight lifting	Swimming and diving	Fencing	Rowing	Cycling	Bowls	Total
Sprained joints												
Shoulder ..			3 (17)	2	4 (21)	2	3 (18)	3 (50)				17 (13)
Elbow			1	2	2		1					6
Wrist			2	1		1	1		1			6
Hand			2	2 (38)	2		3 (18)					16 (12)
Knee	6 (40)	2 (12)	1	2	2	1	1			1	1	17 (13)
Ankle	3 (20)	10 (59)	1	2	2	1	1	1	1			20 (15)
Foot	2 (13)			2	1		2					5
Temporo-mandibular ..				2								2
Neckache ..				2	2	1	2					5
Backache ..	2 (13)	3 (18)	8 (44)	3 (13)	5 (26)	7 (50)	2	2 (33)	2 (50)			34 (25)
Synovitis												
Knee	1	1			1	1	1					5
Ankle	1	1										2
Elbow				1								1
Totals	15 (11)	17 (13)	18 (13)	24 (18)	19 (14)	14 (10)	17 (13)	6 (4)	4 (3)	1 (1)	1 (1)	136 (100)

TABLE V.—VARIOUS INJURIES (Percentages in Parentheses)

	Athletics											
	Running	Jumping	Throwing	Boxing	Wrestling	Weight lifting	Swimming and diving	Fencing	Rowing	Cycling	Bowls	Total
Contusion .	3	4		8 (57)	9 (60)	2	1	1		1		29 (34)
Sore heel .	1	8 (44)										9 (11)
Laceration and abrasion ..	6	3	1	2	6 (40)	1	1	1		4		25 (30)
Blisters	11 (48)	3		2				1				17 (20)
Fractures ..	2			2			1					5
Totals .. .	23 (27)	18 (21)	1 (1)	14 (16)	15 (18)	3 (4)	3 (4)	3 (4)	0	5 (6)	0	85 (100)

Table IV shows the expected preponderance of joint sprains in the upper limb joints in most sports in which these limbs are actively used. With regard to backache and neckache I make no apology for the diagnosis, for a more accurate one is notoriously difficult to make, but as the majority of these lesions appeared to be ligamentous in type they have all been included in this section and comprise 25% of all these joint lesions. Backache seems to have been caused by the rotational strains applied in throwing, wrestling and boxing as well as by extension strains in weight-lifting and diving. The two body contact sports, boxing and wrestling, produced the highest percentages of joint injuries, but were closely followed by jumping, throwing, swimming, running and weight-lifting. Sprains of the ankle-joints were the highest in jumpers, the history was nearly always of their occurrence on landing awkwardly. However, knee sprains were remark-

TABLE VI

	Total no. of athletes	Muscle and tendon strains	Rate/100 athletes	Joint sprains	Rate/100 athletes	Various injuries	Rate/100 athletes	All injuries Rate/100 athletes
Running	234	67	28·6	15	6·4	23	9·8	44·8
Jumping	127	29	22·8	17	13·4	18	14·2	50·4
Throwing	63	12	19·0	18	28·6	1	1·6	49·2
Boxing	98	6	6·1	24	24·5	14	14·3	44·9
Wrestling	59	14	23·7	19	32·2	15	25·4	81·3
Weight lifting ..	67	6	9·0	14	20·9	3	4·5	34·4
Swimming and diving	148	16	10·8	17	11·5	3	2·0	24·3
Fencing	60	12	20·0	6	10·0	3	5·0	35·0
Rowing	101	7	6·9	4	4·0	0	0·0	10·9
Cycling	82	2	2·4	1	1·2	5	6·1	9·7
Bowls	83	0	0·0	1	1·2	0	0·0	1·2
Totals	1,122	171	15·2	136	12·1	85	7·6	34·9

ably few in jumpers and unexpectedly high in runners, the reason for which I do not know. Boxers showed a fairly even distribution of joint lesions apart from those of the hands and fingers.

Of the various injuries in Table V contusions were not unnaturally highest in boxers and wrestlers, the sore heel pad was almost entirely confined to jumpers who bruise their heels on landing. The incidence of lacerations and abrasions indicates that runners and jumpers occasionally fell over and cyclists fell off their cycles, whilst among wrestlers these lesions were mainly due to "mat burns" The blisters amongst the runners were nearly all in marathon runners.

Table VI summarizes the incidence of these three groups of hazards in the various sports and gives the injury rate for every 100 competitors at risk in each sport for this four-week period of training and competition. The true rates were probably higher than those given, for not all the teams, including big contingents from the four home countries, were in residence for the full four weeks; no adjustment has been made for this factor.

Wrestlers had the highest rate for joint sprains and "various" injuries and the second highest rate for muscle strains; these consistently high figures for all types of injury made wrestling easily the most hazardous of these sports. Jumping was next, following the same pattern of a high figure for each injury group. Throwing was the next hazardous; it is evident that this sport traumatizes the joint ligaments more than the muscles, as also does boxing. The incidence of muscle and tendon lesions amongst runners has already been referred to, 28% of them reported such lesions during this four-week period.

TREATMENT

Firstly I must point out that if one divides the tearing of muscle, tendon or ligament into two big categories, namely partial or complete tears, then none of the joint ligament sprains seen was considered to be complete and only two of the muscle tears involved any great bulk of tissue. Tearing involves not only rupture of tissue but hæmorrhage and possibly hæmatoma formation, a traumatic inflammatory reaction results and repair commences by absorption of the effusion followed by fibroblastic proliferation.

Treatment of these lesions was upon generally accepted principles, namely by the first-aid application of cold and pressure and sometimes limiting movement in order to control further hæmorrhage. Once this stage was over various forms of heat, massage and graduated movement were employed to aid absorption of effusion. The last stage involved increasing mobilization of the new scar tissue, usually by the resumption of graduated training. Using these principles and given a reasonable amount of time, healing of the vast majority of strains and sprains that we encountered would have been uneventful. However, as always in athletic injuries, time is at a premium. Almost the first question an injured athlete asks is "When do you think I will be fit to compete again"?

This constant stimulus is always behind those of us who deal with athletic injuries and the question of the value of local hydrocortisone infiltrations in shortening the time required for healing is one upon which there is at present no accord. By this method we treated many sprains and strains in all stages of healing, but never earlier than thirty-six hours from the occurrence of the lesion. When an athlete felt he could compete with an incompletely healed lesion and we thought it safe for him to do so, then pre-competition hydrocortisone or procaine and hydrocortisone were given.

Under the circumstances prevailing it was obviously impossible to undertake any sort of controlled trial on the effects of hydrocortisone for although some cases were treated by local hydrocortisone only, many others had physiotherapy in addition. I therefore have only clinical impressions to relate.

However, there is no doubt in my mind that, for minor joint sprains and more severe sprains in the later stages of healing, local hydrocortisone is a most effective form of treatment. Most joint ligaments are readily accessible to the injecting needle and sufficiently superficial for one to be reasonably certain that the hydrocortisone is in

fact put in and around the ligament. In traumatic synovitis, although we only had a few such lesions, usually one intra-articular hydrocortisone injection had a miraculous effect which was sustained. That it was sustained is not very remarkable for the cause of the inflammation was no longer present; in contrast to the more common use of intra-articular hydrocortisone in chronic arthritis.

Of the muscle strains the same cannot be said; a few responded spectacularly, some showed partial improvement and others showed no significant improvement. These results do not necessarily mean that hydrocortisone is no good in muscle strains for there is a potent technical consideration that should not be overlooked. This is the difficulty of putting the hydrocortisone into the right place, which is fairly easy to do if the strain is a superficial one, but it is exceedingly difficult to inject the hydrocortisone at the right point and right depth when the strain is somewere in the middle of a large muscle belly.

In most of these injections into muscle or ligament I mixed a small quantity of local anæsthetic with the hydrocortisone to act as an "indicator". If after the injection pain was temporarily abolished then one felt fairly sure that the hydrocortisone, too, was in the right place. This method works, for a good immediate anæsthetic effect from the procaine generally indicated subsequent good effect twelve to forty-eight hours later attributable to the hydrocortisone.

Of the tendon lesions the few cases of tennis elbow responded well to this treatment but not so the sore tendo achillis and in many of them only partial immediate anæsthesia was obtained and the ultimate results were uniformly poor. The condition does not respond to rest or physiotherapy and in fact we found no satisfactory treatment for this condition.

Another point worth consideration is that muscle strains may be of two types, namely those of the muscle fibres themselves and those of any portion of the vast connective tissue framework of the whole muscle. Both types present with pain and localized tenderness but in the latter the major pain is elicited by passively putting the muscle on the stretch, yet active resisted isometric contraction produces far less pain; in the former type the reverse holds good.

Both Thorndike (1948) and Oldfield (1948) have described tears of the external muscle sheath giving rise to obvious subcutaneous muscle herniæ; only two cases presented with this type of lesion.

Prevention

The possible cause of the high incidence of muscle strains amongst runners supposedly in the peak of condition deserves consideration. We know that it cannot be inadequate "warming up" before competition for this process is universally practised by athletes with a ritual assiduity. However, Karpovich and Hale (1956) reported that the effect of "warming up" either by preliminary exercise, deep or light massage did not improve physical performance as measured by a limited set of performance tests. Nevertheless it is well established that exercise increases the blood supply to muscle as compared with its resting state which must be an advantage to, say, a sprinter starting. Further support for this practice is seen in the "warming up" of racehorses before a race.

The next consideration is whether muscle strains can be due to defective training. The basic concept of training is that structure becomes adapted to the function demanded of it provided the demand is repetitive. In training the demand is gradually increased and function eventually enormously increased as compared with the pre-training state. Theoretically there is no limit to improvement in function, although the increments become smaller and smaller as efficiency increases. This applies to all systems of the body between which, of course, there is a high degree of integration and for basic training the modern athlete sets out to train his cardiovascular system, lungs, nervous system, muscles, ligaments, &c., with equal efficacy, finally concentrating on the particular aspect demanded for the sport in which he is interested. It may be sheer brawn as in weight-lifting, it may be brawn plus speed of contraction as in putting the shot, or agility in high-jumping, or endurance in distance running, and so on. But one thing is certain: whatever the particular attributes desirable for a particular sport, they have to be married to a skill and if skill is not trained at the same rate then the athlete will be liable to injure his muscles or joints through faulty technique. This is, I believe, the basic cause of the vast majority of such injuries and so their prevention lies with the athlete and his coach to develop technique and skill at a rate commensurate with physical development.

This dictum does not apply with such force to body contact sports but even here I think that Tucker (1954) has made a good case for the "alerted posture" as a means of avoiding injury. Briefly the "alerted posture" means alerting the prime fixer muscles so that quick movements can be carried out by activators and synergists acting on a frame already made firm by the prime fixers.

However, defective skill is not the full answer to why runners tear their hamstrings and less frequently their quadriceps. I have already referred to the absence of muscle strains in the cyclists and rowers, yet the legs are used a great deal in both

these sports. However, the rate of muscular contraction although reasonably fast in these sports is not ultra-rapid as in sprinting and not quite as fast as in middle distance running. Furthermore in weight-lifting muscular action is not ultra-rapid and weight-lifters produced a relatively low rate (9·0%) of muscle strains as compared with runners (28·6%). It seems that speed of muscular contraction is a greater factor than actual work done during contraction in the production of muscle injury. Hill (1927) has shown that if a muscle shortens quickly it does less work than if it shortens slowly, consequently if the same external work has to be done quick movements require the excitation of more muscle fibres. In accelerating a sprinter from zero to his maximum velocity the leg muscles are almost certainly developing their maximum power at this very rapid speed of contraction. Now when a muscle is fully stretched greater contractile power is possible but also greater power is required to overcome frictional resistance resulting from the changing shape of the muscle. I think that the brief time when rapid maximum contraction is demanded of a fully stretched muscle is the point at which that muscle is likely to tear.

Such a state of affairs exists in the hamstrings of a sprinter when the trailing leg is fully extended and is on the point of being lifted and brought forward by flexion at the knee and hip. In Fig. 1, which shows three sprinters, the trailing leg of each should be noted, for No. 18's is fully extended, that of No. 66 half flexed at the knee and that of No. 14 is optimally flexed for the leg to be brought right through. Tearing of the hamstrings is likely to occur at a stage between the position of the leg of No. 18 and No. 66. In Fig. 2 the trailing leg is at an earlier stage in the cycle than that of No. 18 in Fig. 1, for the extensor drive is not quite complete, but already the hamstring tendons can be seen to be taut. Fig. 3 runner No. 12, illustrates this point again.

FIG. 1.

FIG. 2.

MUSCLE SORENESS

The cause of muscle soreness which occurs after prolonged intensive or unaccustomed work has long been a matter of debate. This soreness does not develop until some hours after exercise and may persist for some days. If exercise is resumed when the soreness is still present the symptom will be exacerbated to begin with and then it will slowly disappear only to appear again after the exercise is finished.

One explanation is that muscle fibres have been ruptured but, against this, quite mild but repetitive activity in an untrained muscle will produce soreness. Chemical explanations have therefore been put forward, one of them being that it is due to lactic acid persisting in the muscles. However, the lactic acid content of a muscle is highest during its greatest activity whilst in the ensuing hours following cessation of activity the lactic acid level falls rapidly just when muscle stiffness is appear-

ing, so that this seems unlikely to be the cause.

Karpovich (1953) believes that the probable explanation lies in an altered permeability of the sarcolemma of untrained muscle fibres following exercise, which gives rise to water retention within the fibres causing swelling of the muscle and compression of sensory nerve endings.

Two of the cases that I have classified under strains of the anterior tibial group of muscles deserve special mention in this respect. Both were marathon runners from small countries where no very great competition at this enormous distance was to be had and there was presumptive evidence that both athletes were short of training by first-class standards. Both reported complaining of undue soreness in the anterior tibial compartment of one leg and both reported during the pre-competition training period. Examination showed that there was slight but definite swelling over the antero-lateral aspect of the leg in question and palpation revealed that the anterior tibial group was unduly firm as compared with that of the unaffected leg, but no crepitus was elicited on movement and there was no evidence of nerve lesion. Both cases were admitted to hospital and the leg rested in elevation; in both the signs subsided in forty-eight hours but returned again some days later on the resumption of training.

Copyright *Western Mail and Echo*, Cardiff.

FIG. 3.

It seems likely that these were examples of the early phases of the so-called "anterior tibial syndrome" described by Barham Carter *et al.* (1949) as occurring in young persons after unaccustomed strenuous activity. Biopsy in Barham Carter's cases showed necrosis of and hæmorrhage into muscle, granulation tissue and fibrosis; there was also a lateral popliteal nerve lesion thought to be a secondary phenomenon resulting from pressure of the brawny swelling that filled the area.

The two cases described would seem to add support to the hypothesis of Karpovich as to the cause of muscle soreness as well as indicating that the "anterior tibial syndrome" might be a gross form of this same phenomenon.

CONCLUSION

Our discipline in medicine is concerned with the application of physical methods in restoring the subnormal to normal, or as near normal as possible. My reason for choosing this subject for my Address is to encourage more interest in the supernormal who has become only normal or slightly subnormal through injury. We are so concerned in our clinics with the grossly subnormal, that the supernormal, only slightly disabled by usual standards, is apt to receive scant attention, yet to the athlete himself a slight disability means a great deal.

REFERENCES

CARTER, A. B., RICHARDS, R. L., and ZACHARY, R. B. (1949) *Lancet*, ii, 928.

FELL, W. A. (1956) *Proc. R. Soc. Med.*, **49**, 445.

HILL, A. V. (1927) Muscular Movement in Man. New York; p. 45.

KARPOVICH, P. V., Ed. (1953) Schneider's Physiology of Muscular Activity. 4th ed. Philadelphia and London; p. 25.

——, and HALE, C. J. (1956) *J. Amer. med. Ass.*, **162**, 1117.

OLDFIELD, M. C. (1948) *Brit. J. Surg.*, **36**, 405.

THORNDIKE, A. (1948) Athletic Injuries. 3rd ed. London; p. 81.

—— (1956) *J. Amer. med. Ass.*, **162**, 1126.

TUCKER, W. E. (1954) *J.R. Inst. publ. Hlth.*, **17**, 245.

WYNN-PARRY, C. B. (1956) *Proc. R. Soc. Med.*, **49**, 446.

BOOKS RECEIVED FOR REVIEW

Ambrose (G.), and Newbold (G.). A handbook of medical hypnosis. 2nd ed. pp. xiii + 276. London: Baillière, Tindall & Cox. 27s. 6d. 1958.

Bartrán (R. P.). Contribución al estudio de las demencias preseniles (enfermedades de Alzheimer y Pick). Published in Informaciones Psiquiatricas, Vol. III, No. 1, 1958. pp. 135. Barcelona. 1958.

Bayer (O.), and Wolter (H. H.). Atlas intracardialer Druckkurven. English translation by G. R. Graham. Spanish translation by E. Low-Maus. pp. 186. Stuttgart: Thieme. DM.68. 1959.

Boyd (B. F.). Highlights of Ophthalmology 1958. Vol. II, Nos. 1, 2 and 3; 2nd ed. pp. xix + 281. Panama. $9.0. 1958.

Bramwell (C.). A clinical introduction to heart disease. pp. 229. London: Oxford U.P. 21s. 1959.

Congresses: Poliomyelitis. Papers and discussions presented at the Fourth International Poliomyelitis Conference. Compiled and edited for the International Poliomyelitis Congress. pp. xviii + 684. Philadelphia and Montreal: Lippincott. 60s. 1958.

Crue (B. L.). Medulloblastoma. pp. x + 206. Springfield, Ill.: Thomas. Oxford: Blackwell. 43s. 1958.

DeJong (R. N.). The neurologic examination. 2nd ed. pp. xv + 1078. London: Pitman. £7. 1958.

Ekstein (R.), and Wallerstein (R.). The teaching and learning of psychotherapy. pp. xvi + 334. London: Imago. 42s. 1958.

Gaddum (J. H.). Pharmacology. 5th ed. pp. xvi + 587. London: Oxford U.P. 42s. 1959.

Hunter (D.). Health in industry. pp. 288. Harmondsworth, Middx.: Penguin Books Ltd. 4s. 1959.

Paul (J.). Cell and tissue culture. pp. viii + 261. Edinburgh and London: Livingstone. 30s. 1959.

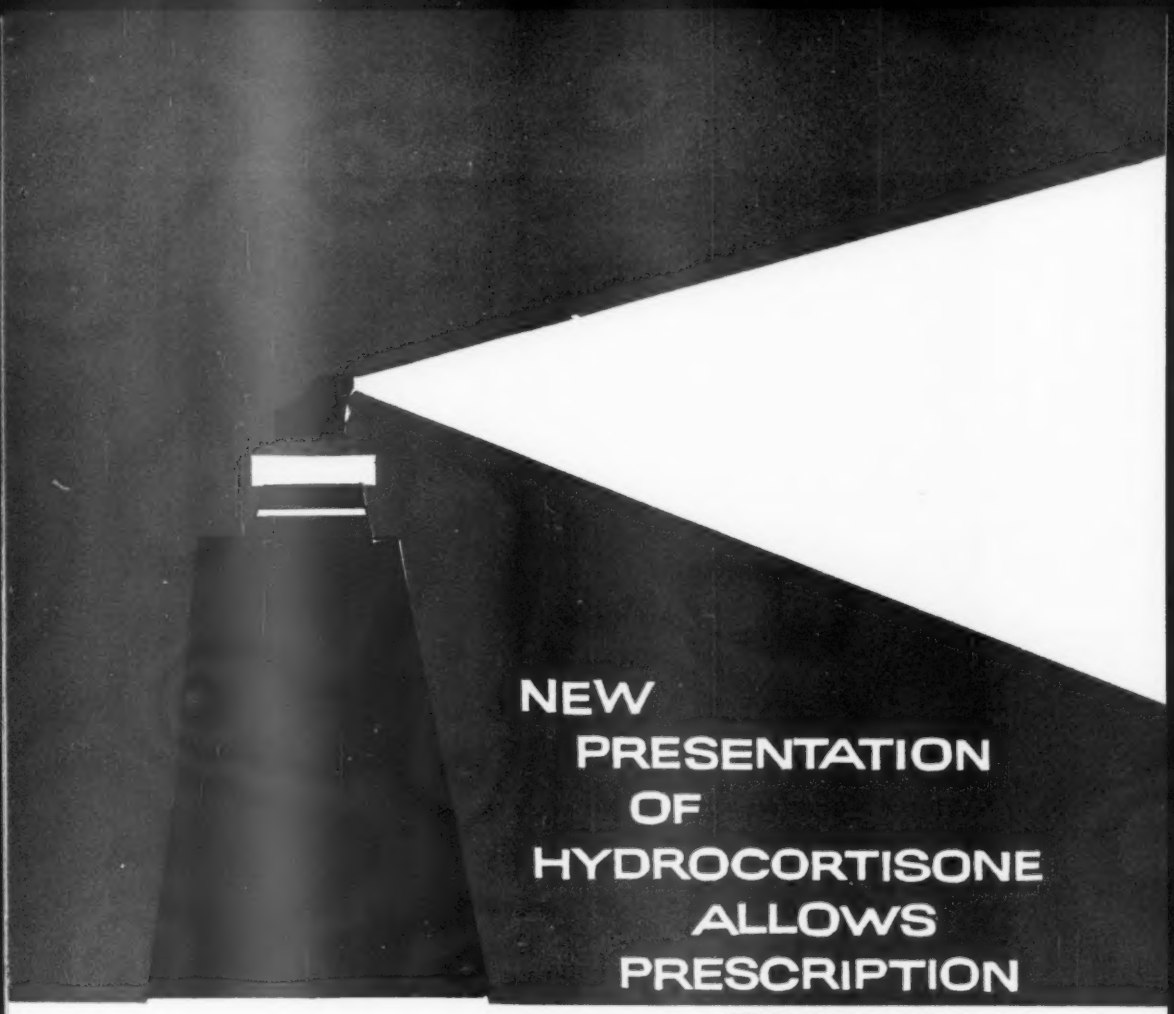
Pemberton (J.), and Willard (H.), eds. Recent studies in epidemiology. pp. xiii + 203. Oxford: Blackwell. 25s. 1958.

Poynter (F. N. L.), ed. The history and philosophy of knowledge of the brain and its functions. An Anglo-American Symposium, London, July 15–17, 1957. pp. x + 272. Oxford: Blackwell. 22s. 6d. 1958.

Pryor (W. J.). A manual of anæsthetic techniques. 2nd ed. pp. viii + 228. Bristol: Wright. 27s. 6d. 1959.

Roxburgh's Common Skin Diseases. Revised by Peter Borrie. 11th ed. pp. xxiii + 495. London: Lewis. £1 17s. 6d. 1959.

Studies on Fertility 1958. Being Volume X of the Proceedings of the Society for the Study of Fertility. pp. x + 176. Oxford: Blackwell. 25s. 1958.



NEW PRESENTATION OF HYDROCORTISONE ALLOWS PRESCRIPTION ECONOMY

Cortril Spray adds economy to the proved effectiveness of topically applied hydrocortisone. It obviates experiments to find the correct presentation of hydrocortisone for a particular case. It saves the wastage of prescriptions part-used because of unsuitable strength or base. Cortril Spray is the only single preparation suitable for all non-infected dermatoses: moist and weeping or dry and scaling.

Cortril* spray

brand of hydrocortisone

PRESENTATION Plastic coated glass bottles containing 100mg. hydrocortisone free alcohol for spray application.

ADMINISTRATION Cortril Spray may be used four or five times a day until the inflammation subsides. For maintenance Cortril Spray should be used once or twice a day. The instructions on the pack should be noted by the patient: shake before use, keep away from direct heat, for external use only, do not spray near the eyes.

SCIENCE FOR THE WORLD'S WELL-BEING

Pfizer

Pfizer Limited, Folkestone, Kent

* Trade Mark

3185

Circular booms or "sacks" each consisting of about 25,000 logs, on the Gatineau River, Quebec, one of Canada's richest sources of pulp wood. *(Photograph by courtesy of the National Film Board of Canada.)*

Proceedings of the Royal Society of Medicine

Vol. 52
159

Section of Medicine

President—A. H. DOUTHWAITE, M.D., F.R.C.P.

Meeting
November 25, 1958

DISCUSSION ON PERIPHERAL ARTERIAL DISEASE

Dr. A. L. Jacobs (London):

Medical Aspects of Arterial Embolism

This paper reports some of the results of a study of 69 patients, mainly at the Whittington Hospital, with a total of 122 separate incidents of limb embolism.

Many patients with heart disease suffer embolism in the limbs and recover spontaneously. The limb pulses were examined in 269 patients with mitral stenosis and in 300 controls (paired for sex and age). Old occlusions were found in 27% of those with auricular fibrillation, in 4% of those with regular rhythm and in 0·6% of controls. This is consistent with the incidence of visceral embolism at autopsy.

Ætiology.—The incidence of limb embolism in patients with heart disease increases with increasing age. Auricular fibrillation was the chief ætiological factor (91 incidents). 64 incidents occurred in mitral stenosis, 13 in bacterial endocarditis and 9 in myocardial infarction. Embolism occurred much more frequently at rest than during activity. 13 incidents occurred in close relation to overdosage of digitalis.

Consecutive thrombosis.—The full extent of the consecutive thrombus was determined by post-mortem dissection in 64 embolized limbs. Thrombosis reaching the next main bifurcation beyond the embolus was classified as "major", thrombosis of lesser extent as "minor". Gangrene was not significantly more common in the group with "major" thrombosis. Some limbs with very extensive thrombosis survived and a few with little or no thrombosis became gangrenous. The commonly held view of the danger of consecutive thrombosis perhaps needs revision.

Symptoms.—The common symptoms were pain, subjective coldness, numbness, loss of power and tingling of the extremity. Pain of distal type was recorded in 71% of incidents; 15% also had transient pain in the region of the occlusion. The onset of symptoms was gradual in 21%. In a small number of occlusions (all aortic or iliac) there were general symptoms, superficially resembling surgical shock but in these patients the blood pressure was usually *raised* above normal level.

Arterial pulsation.—Among 47 embolic occlusions seen within twenty-four hours of onset of symptoms there were 12 in which pulsation (almost invariably weakened) could be felt distal to the embolus. 8 of these were in the aorta or the iliac artery. In localizing an embolus, therefore, *weakened* pulsation has the same significance as *absent* pulsation.

Diagnosis.—Any acute ischæmic syndrome in a limb, occurring in a patient with heart disease, should be regarded as embolic. If this rule is followed, errors will not be numerous. One source of error is so-called "pseudo-embolism", which seems to occur mainly in patients with heart disease and which mimics embolic occlusion perfectly. There were 4 examples of pseudo-embolism, 2 of them subsequently verified by careful arterial examination at autopsy. This condition is probably due to some lesion of the arterial wall with resultant arterial spasm. There seems to be no way of distinguishing it clinically from true embolism, except by arteriography.

Outcome.—Survival of the limb is relatively common, but it is not yet established how far outcome may be influenced by treatment. For comparative purposes the "limb survival rate" (L.S.R.) was used, i.e. the proportion of incidents in which the limb survives, expressed as a percentage of all incidents in the group (including indeterminate incidents). Table I shows the overall results in 115 incidents. The L.S.R. varies inversely with the size of the artery occluded. No instance of gangrene was seen in brachial embolism and only 2 instances in popliteal embolism; both the latter cases were moribund from other causes when gangrene developed. Fig. 1 illustrates an example of popliteal embolism, discovered only by routine examination of the limb pulses. Autopsy and post-mortem arteriography were performed nine months later. On the side with the popliteal occlusion, injection of the leg and foot is as full

TABLE I.—115 EMBOLIC INCIDENTS—LIMB SURVIVAL RATES

Site of embolism	Total	Limb survival rate 25% 50% 75%
Axillary ..	8	75%
Brachial ..	14	86%
Aortic ..	17	24%
Iliac	25	52%
Femoral ..	24	75%
Popliteal ..	27	89%
All sites ..	115	67%

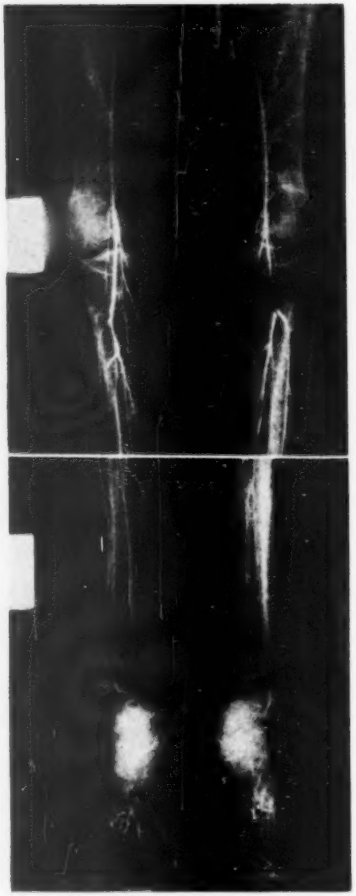


FIG. 1.—Embolism of left popliteal artery. Post-mortem arteriography, performed nine months after clinical diagnosis.

as that on the sound side. Moreover, the vascular pattern in the embolized limb shows none of the arterial proliferation usually seen in chronically ischæmic limbs, which suggests that the natural endowment of arterial collaterals was adequate without further development.

TABLE II.—LIMB SURVIVAL RATES IN TREATED AND UNTREATED EMBOLISM

Site of embolism	Treated		Untreated	
	Total	L.S.R.	Total	L.S.R.
All sites ..	41	56%	68	74%
Aortic Iliac Femoral	24	46%	37	57%

Effect of treatment on outcome.—Table II shows the outcome in 109 incidents which had no operation. 41 were treated, mainly by anticoagulants and vasodilator methods; 68 had only palliative treatment. The L.S.R. is a little *lower* in the treated group. If the results in cases diagnosed within ten hours of onset are compared with those of cases diagnosed later, there appears to be an advantage with the early treated cases, especially in the group aortic, iliac and femoral embolism. However, the L.S.R., even in this group (60%), is not significantly higher than that of untreated embolism (57%).

Results of surgical treatment.—This series contains only 6 cases treated by embolectomy but examination of 7 well-known collected series of embolectomies shows only one (Warren *et al.*, 1954) claiming a limb survival rate of more than 50% for lower limbs (Petitpierre, 1928; Danzis, 1933; Pearse, 1933; Strömbeck, 1935; Key, 1936; Lund, 1937; Warren *et al.*, 1954). The corresponding figure for untreated embolism is 71%. No doubt treated series contain a higher proportion of the more grave ischæmic syndromes than untreated series and this probably explains the lower limb survival rates.

It must not be concluded from these figures that embolectomy never averts gangrene, but the number of successes must be small—too small to affect the overall results of a large series. Nevertheless, embolectomy is probably the most effective treatment available and its indications must be clearly established.

Prognosis and indications for embolectomy.—In brachial and popliteal embolism, embolectomy should rarely be required. In aortic embolism, natural recovery is not very likely and there is also a special difficulty, for some cases which at first appear to be improving suddenly regress and develop gangrene. In the early stages there is no way of predicting this and the only safe rule is to operate at once on any case of aortic embolism seen early enough.

In iliac, femoral and axillary embolism, the problem is to recognize in the early stages those limbs which have no chance of recovery without operation. Some observers advocate a trial period of medical treatment but a delay of two or three hours is not to be lightly accepted, especially if the effectiveness of medical treatment is so much in doubt.

Correlation of the early signs with the subsequent fate of the limb showed that if the limb is going to survive obvious improvement in the ischæmic signs will occur within two hours of the onset of symptoms. If signs of grave ischæmia are still present after this then gangrene is very probable.

Three signs were found to be useful in assessing the gravity of the ischæmia:

(1) Pallor of the whole foot or hand.
(2) Sensory impairment of the whole foot or hand.
(3) Emptiness of the superficial veins of the foot or hand, or very sluggish refilling after expression.

If these signs are still present two hours after onset they indicate probable gangrene (*see* Table III). The bias in favour of operation will naturally be strongest in iliac embolism.

TABLE III.—PALLOR OF WHOLE FOOT OR HAND AS PROGNOSTIC SIGN

31 Limbs, All Seen Within Ten Hours of Onset

Time after onset	Limbs which survived		Limbs which necrosed	
	Total	No. with this sign	Total	No. with this sign
0–2 hours ..	10	7	1	1
2–10 hours ..	11	—	9	6

Arterial spasm in embolism.—Many of the statements made about embolic arteriospasm do not seem to be well substantiated. For example, it has been said that arterial spasm may produce ischæmic signs of such extent as to give a false impression of the height of the occlusion (De Takats, 1942; Leriche, 1947; Holden, 1952). Records of the extent of the ischæmic signs were made in 19 examples of lower limb embolism, all seen within twenty-four hours of onset and all anatomically verified. In every instance the upper limit of the ischæmic signs was well below the level of the embolus.

The only satisfactory clinical evidence of arterial spasm is suppression of pulsation *proximal* to the embolus. In 40 anatomically verified incidents there was only one in which pulses proximal to the embolus were suppressed. This was a case of popliteal embolism with suppression of the femoral pulse at the groin. The effect appears to have been due to arterial spasm but this could not have affected the collaterals, for the ischæmic signs were mild, though the femoral pulse did not return for ten days. This case represents the only clinical evidence of arterial spasm in the whole study. Embolic arterial spasm seems to be a rare phenomenon and its importance has been much exaggerated.

Anatomical factors.—The L.S.R. varies inversely with the size of the artery occluded but this does not explain why gangrene occurs in any particular case. Obviously, the state of the general circulation must be an important factor. There has been much preoccupation with local vasomotor reactions in the limb but less attention has been paid to the possibility of anatomical deficiency of arterial anastomoses. Anatomical information on this subject is scanty but some investigations (e.g. Olovson, 1941) indicate that there are some persons with deficiency of arterial collaterals. A comparative study of arterial collaterals by post-mortem arteriography in a series of 66 human subjects showed that deficiency of collaterals is not uncommon in the femoral system, whereas it is rare in the brachial and popliteal systems. This agrees with clinical experience of the incidence of gangrene. Anatomical factors are probably much more important than local vasomotor reactions in deciding the fate of the limb. This would explain the unimpressive results of medical treatment.

Clinical management.—The most important medical measure is treatment of the heart disease, avoiding overdosage of digitalis and using diuretics with discretion, for hæmoconcentration may cause new intracardiac thrombosis and so provoke further embolism. Anticoagulants probably have little effect on the local result in the limb but they may help to reduce the risk of further embolism. Vasodilator drugs and warming the patient's torso may be harmful, for these measures can only produce *general* vasodilatation and so lower the blood pressure. The only vasodilator method free from this objection is injection of the regional sympathetic ganglia. Most of the figures quoted in support of medical treatment can be explained by natural recovery.

Embolectomy is probably the only effective treatment. In the patient with severe ischæmic signs, persisting for two hours after onset, operation should be performed without delay.

REFERENCES

DANZIS, M. (1933) *Ann. Surg.*, **98**, 249, 422.
DE TAKATS, G. (1942) *Surg. Clin. N. Amer.*, **22**, 199.
HOLDEN, W. D. (1952) Acute Peripheral Arterial Occlusion. Springfield, Ill.
KEY, E. (1936) *Brit. J. Surg.*, **24**, 350.
LERICHE, R. (1947) Les Embolies de l'Artère Pulmonaire et des Artères des Membres. Paris.
LUND, C. C. (1937) *Ann. Surg.*, **106**, 880.
OLOVSON, T. (1941) *Acta chir. scand.*, **86**, suppl. 67.
PEARSE, H. E., Jr. (1933) *Ann. Surg.*, **98**, 17.
PETITPIERRE, M. (1928) *Schweiz. med. Wschr.*, **28**, 700.
STRÖMBECK, J. P. (1935) *Acta chir. scand.*, **77**, 229.
WARREN, R., LINTON, R. R., and SCANNELL, J. G. (1954) *Ann. Surg.*, **140**, 311.

Dr. David Sutton (London):

Percutaneous Arteriography in Peripheral Vascular Disease

My contribution to this discussion on peripheral vascular disease consists mainly of a brief review of my arteriographic material over the past eight years. This material has been seen in the Diagnostic X-ray Departments at St. Mary's Hospital, and at Maida Vale Hospital for Nervous Diseases. The total material consists of 5,870 arteriograms (Table I). All were performed by percutaneous techniques, either personally or by assistants under supervision.

TABLE I

Total arteriograms 5,870				
			Complications	
		Deaths	Permanent	Temporary
Cerebral				
Carotid ..	3,500	2	—	3
Vertebral ..	350	—	1	—
Aortograms				
Abdominal ..	900	—	—	3
Thoracic ..	50	2	1	1
Peripheral				
Femoral ..	950	—	—	—
Subclavian and brachial	120	—	—	4

Table I shows the distribution of arteriograms by regions. It also lists the major complications which have occurred.

Table II lists the various vascular lesions which may be examined by arteriography in the investigation of peripheral vascular disease.

TABLE II

(1) Atheromatous stenosis and thrombosis
(2) Buerger's disease
(3) Raynaud's phenomenon
(4) Embolus
(5) Aneurysms
(6) Arteriovenous malformations
(7) Traumatic lesions (arteriovenous fistula, traumatic thrombosis)
(8) Congenital anomalies

(1) *Atheromatous stenosis and thrombosis.*—Arteriography and clinical studies in the last ten years have made it quite clear that atheromatous disease is the major cause of arterial thrombosis in peripheral vascular disease. Certain sites of election and their associated clinical syndromes are now well recognized. These sites of election for atheromatous thrombosis are: (*a*) The femoral artery. (*b*) The popliteal artery. (*c*) The iliac artery. (*d*) The abdominal aorta. (*e*) The carotid bifurcation. (*f*) The calf vessels—occlusions here are nearly always associated with lesions in a major vessel such as the femoral.

In all these regions atheromatous irregularity and narrowing of the lumen is eventually followed by complete thrombosis. The approximate incidence of complete thrombosis, or major stenosis producing clinical symptoms of peripheral vascular disease, in our series has been as follows:

Femoral and popliteal arteries ..	800 cases
Iliac artery	200 ,,
Abdominal aorta	50 ,,
Carotid artery	100 ,,

In many cases of femoral, iliac, and aortic thrombosis, distal occlusions were also present.

I think these figures give a fair idea of the relative incidence and frequency of symptom-producing atheroma in the major peripheral vessels as seen at large vascular and neurological clinics.

Atheromatous stenosis or thrombosis in the upper limbs is of course relatively rare, but we do see occasional cases. Atheromatous stenosis of a renal artery is now recognized as an important cause of hypertension. We have diagnosed a number of these cases by aortography, and they will be described in a future communication.

(2) *Buerger's disease* used to be given great prominence in medical textbooks as a cause of intermittent claudication. It is now well known that many cases previously labelled Buerger's disease were in fact cases of atheromatous thrombosis of the femoral artery. However, occasional cases are seen which fulfil clinically and angiographically the criteria expected of Buerger's disease. They occur in a relatively younger age group—many of our cases have been in their twenties or thirties. There is often a significant history of attacks of "phlebitis". Finally, arteriography shows an appearance quite different from that of the atheromatous vascular disease, and which is virtually diagnostic. This consists of a distal obliteration of the arteries, commencing in the foot vessels and slowly extending into the calf vessels. In a typical case, angiography will show a normal femoral and popliteal artery, and probably the upper portions of the anterior tibial, posterior tibial, and peroneal arteries will also appear normal. Their distal portions, however, will be completely obliterated and the circulation to the foot will be carried by small spiral muscular anastomotic vessels. In the later stage the disease process may ascend proximally and involve the popliteal and even the femoral artery. In rare cases the upper limb may also become involved.

In our material about 3 or 4% of femoral arteriograms have shown these arteriographic appearances consistent with the diagnosis of Buerger's disease. I must repeat, however, that atheromatous vascular disease has proved to be the cause of the symptoms in over 90% of our cases with symptoms of arterial insufficiency in the lower limbs, and is undoubtedly the major cause of peripheral vascular disease in clinical practice.

(3) In the upper limbs *Raynaud's phenomenon* is the commonest form of peripheral vascular disease investigated by angiography. Arteriography in cases of so-called primary Raynaud's phenomenon merely shows narrowed digital vessels with poor blood supply to the fingers.

Arteriography is a more important investigation in the assessment of cases of Raynaud's phenomenon secondary to lesions of the major vessels.

(4) *Embolus.*—Surgery when carried out is usually a matter of emergency. If there is any clinical doubt about the level of the block, arteriography will demonstrate it conclusively. In our

material we have had the opportunity of performing arteriograms on some 30 cases of embolus. Most of these lay in the popliteal artery, but we have also seen emboli presenting in the iliac artery, and in the superficial femoral artery. In 2 cases we have seen the profunda occluded. In 1 of these cases this was associated with popliteal, and the other with femoral artery occlusion.

Blockage of the profunda which is the main source of collaterals in the lower limb naturally makes the prognosis much graver.

In the upper limb we have encountered embolic occlusion of both the brachial and the radial artery. In the few cases of cerebral embolus investigated the occlusion in each case lay in the middle cerebral artery.

Fig. 1A shows the appearance of a popliteal embolus. This occurred in a patient gravely ill following a coronary occlusion. It responded remarkably well to medical treatment, and a later arteriogram (Fig. 1B) shows a surprisingly normal appearance. Whilst discussing emboli it should be mentioned that we have now seen 6 cases of the Leriche syndrome, or aortic thrombosis, in patients with mitral disease and auricular fibrillation. In all these cases the lesion seems to have developed insidiously following peripheral emboli in one or other limb.

Fig. 2 shows a femoral arteriogram in a case of peripheral embolus. It demonstrates the unusual and interesting feature of "beaded spasm" of the femoral artery. An illustration of this phenomenon has been published by Wickbom and Bartley (1957). Personally, I have noted it in my material about ten times. In all but one of my cases this "beaded spasm" occurred in the vessels to the lower limb, the exception being a case where a similar appearance was observed in the carotid artery in association with a carotid thrombosis in the cavernous sinus. In the lower limbs it is of interest that I have seen it twice in association with embolus, and twice in association with Buerger's disease. Most of my cases showed this beaded spasm in the femoral artery, but I have also seen it in the calf vessels and in the common iliac artery.

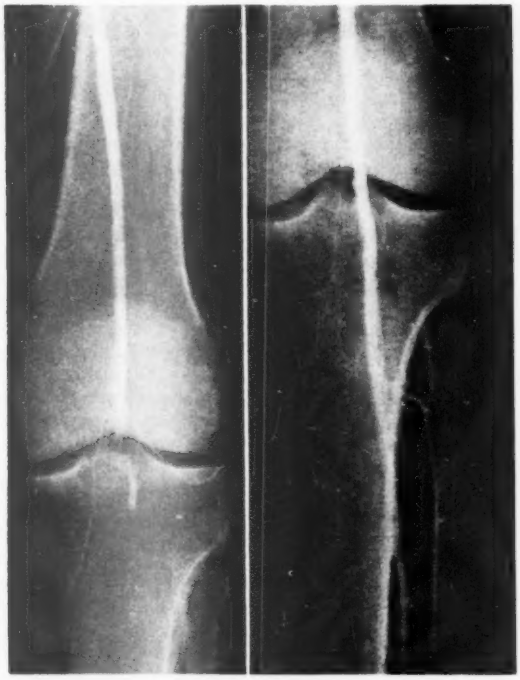


FIG. 1A.—Arteriogram showing embolus occluding the popliteal artery at the level of the knee-joint.

FIG. 1B.—Arteriogram in same patient following successful medical treatment.

FIG. 2.—Arteriogram showing "beaded spasm" in the femoral artery in a patient with a popliteal embolus.

(5) *Aneurysms* are well demonstrated by arteriography and like the atheromatous lesions have certain sites of election. My material includes over 400 cases.

Some 250 of these lay in the cerebral circulation, and of these the majority lay in the carotid circulation, and were shown by carotid angiography. Only 12 lay in the vertebro-basilar circulation and were shown by vertebral angiography, but with the increasing use of vertebral angiography the proportion of vertebro-basilar aneurysms will undoubtedly rise.

In other regions the figures were as follows:

Abdomen.—About 100 aneurysms of the abdominal aorta, and 10 of the iliac arteries have been investigated by lumbar aortography or transfemoral aortic catheterization.

Thorax.—15 aneurysms of the thoracic aorta have been investigated by thoracic aortography.

Popliteal fossa.—Some 30 aneurysms of the popliteal artery have been investigated by femoral angiography.

Miscellaneous.—Aneurysms at other sites investigated by angiography have included the following: (*a*) 10 in the femoral artery (including several in arterial grafts), (*b*) 3 in the cervical carotid artery, (*c*) 3 in the brachial artery, (*d*) 2 in the innominate artery, (*e*) 1 in the subclavian artery.

It is clear from this list that the only common peripheral aneurysm is the popliteal aneurysm. Popliteal aneurysms are important because, as Gifford *et al.* (1953) have shown, unless surgically treated they usually result in loss of the limb.

(6) *Arteriovenous malformations*, also called angiomatous malformations, or congenital angiomata, have been encountered mainly in the cerebral circulation. 120 cases of cerebral angioma were reviewed before the Section of Ophthalmology of the Royal Society of Medicine in November 1956 (Sutton, 1958). Similar angiomata are less often seen elsewhere, but we have encountered examples in the peripheral circulation, in the trunk, and in the neck. Angiography is often the only method of demonstrating the full extent of the arterial blood supply and the venous drainage system of the lesion, and is usually necessary before surgical extirpation can be undertaken.

(7) *Arteriovenous fistulas of traumatic origin* may be seen anywhere in the circulation. In this condition surgical treatment can present formidable and often insuperable problems, and again arteriography is invaluable in the pre-operative assessment of the case. With large arteriovenous fistulas there may be considerable technical difficulties in obtaining adequate films (Sutton, 1956).

Traumatic thrombosis of major vessels has been investigated by arteriography on a number of occasions, and occlusive lesions shown in the femoral, iliac, carotid, and brachial arteries.

(8) *Congenital anomalies of the vascular system* are another field in which arteriography helps to provide a definite diagnosis, or to show the anatomy with the clarity necessary for surgery where this is being considered. Limitations of space prevent me from discussing this subject in more detail.

Complications

Table I lists the major complications which have occurred in my series. It will be seen that these are relatively few and that the most dangerous investigation in our hands, as in the literature generally, appeared to be thoracic aortography (Abrams, 1957). The two deaths from thoracic aortography occurred with patients under general anæsthesia. One of these deaths was considered by the Coroner to be due to so-called vagal inhibition because the patient collapsed immediately following removal of the endotracheal tube. The other patient did not recover from his anæsthetic and died some fourteen hours after the investigation. Both patients had giant syphilitic aneurysms of the aortic arch with aortitis and coronary stenosis but in neither case was the ultimate cause of death discovered. I think there is no doubt that we must regard these cases as arteriography deaths, but I feel that the general anæsthetic was a factor in one of these poor risk cases, and may have contributed to the other.

The 2 deaths attributed to carotid arteriography occurred with comatose patients already gravely ill, and it is difficult to assess the exact significance of arteriography in these deaths. In this respect it is interesting that we have several times prepared to do angiograms on comatose patients who have died before the procedure could be undertaken. In one case a patient died on his way from the ward to the X-ray department. Presumably if death had occurred half an hour later we would have had to attribute it to the angiogram.

Our morbidity generally has been much lower than that described in most papers in the literature. There is no doubt, however, that there are very many serious complications which can arise during arteriography. I believe that many of these complications are preventable and that the highest incidence of accidents occurs with the casual or occasional arteriographer, whether radiologist or surgeon.

Our experience shows that if performed with

technical efficiency, and a full knowledge of the difficulties and hazards, peripheral arteriography provides invaluable diagnostic information which more than justifies the slight risks involved.

[NOTE.—This paper was illustrated with some 40 slides of arteriograms.]

REFERENCES

ABRAMS, H. L. (1957) *Radiology*, **68**, 812.
GIFFORD, R. N., HINES, E. A., and JANES, J. M. (1953) *Surgery*, **284**, 293.
SUTTON, D. (1956) *Proc. R. Soc. Med.*, **49**, 559.
—— (1958) *J. Fac. Radiol.*, **9**, 90.
WICKBOM, I., and BARTLEY, O. (1957) *Acta radiol. Stockh.*, **47**, 433.

Mr. Peter Martin (London):

Surgical Management of Arterial Embolism

The outlook for a patient admitted to hospital with a diagnosis of peripheral embolism is gloomy. He has about a 50% chance of death in hospital. If he lives he has a 25% chance of amputation. Thus, of 38 patients with this diagnosis admitted to one hospital, 18 died, 5 suffered amputation and only 15 were discharged, and of these only 5 had a limb without significant ischæmic symptoms and only 3 had a normal circulation.

It is difficult, and has been unprofitable, to compare the results of medical or surgical treatment for peripheral embolism. It has been the practice in many places for surgery to be offered too late so that results have been most discouraging, but even when the patient has been referred early results have often been disappointing. Physicians have lost confidence in surgery, and surgeons have become disheartened so that excuses to avoid operation have been readily seized. The phrase "limb survival rate" instead of the word "cure" seems to have become the yardstick of success.

The high mortality rate associated with peripheral embolism depends on:

(1) Progressive impairment of cardiac function.

(2) Pulmonary embolism.

(3) Recurrent systemic embolism.

The results of a successful embolectomy are often spoilt by further embolisms at frequent intervals, and then, if indeed they have not taken the patient's life, they cease often for years.

A 38-year-old female patient was operated on for a saddle embolus. The pulses returned. Two days later another embolus lodged at the bifurcation of the left femoral artery and this was removed, with recovery of pulses. Two days later one was removed from the right femoral artery with partial recovery of circulation in that leg. Six days later another embolism occurred in the left femoral. This was removed, but unsuccessfully, and then still a further embolism occurred in the right femoral a week later. Both legs were amputated through the thigh and no further emboli have since been detected. The patient was discharged home.

If recurrent embolism could be avoided by an atrial appendicectomy at the time of the first embolectomy, lives and limbs would be saved. Difficulties of organization would be great and diagnostic exactitudes would be necessary. The concept is an undoubted challenge and one which I believe should be most carefully considered. It is at least one method which holds some promise of improved results.

IMPAIRMENT OF THE CIRCULATION AND GANGRENE

Many embolisms of smaller vessels, especially those of the upper limbs, pass unnoticed. Probably such emboli obstruct these smaller vessels completely, but collateral channels are often adequate and soon function and even pulses return. If a large embolus obstructs completely a major lower limb vessel, sudden acute symptoms occur which may lead to early removal of the embolus and restoration of the circulation. Often, probably more often than not, an embolus only partially obstructs a main vessel so that pieces of clot may break off and be carried by the blood stream to lodge more distally, and the main artery may be obstructed at different sites throughout its length. It may be that sometimes a similar arrangement may arise from multiple emboli arising from the heart. However the emboli arise, each clot may grow a tail of consecutive thrombus and these may join together obliterating a segment of artery. Occasionally, and more fortunately, organization of a partially obstructing clot takes place and the vessel remains patent though permanently narrowed. The fact remains that, in most of those which come to surgery, emboli together with consecutive clot fill segmentally or completely the main vessel of the limb. Therefore, removal of an embolus, with or without consecutive clot, from the common femoral artery for example, is by no means all that is necessary for cure, because a further distal embolus is highly probable.

In review, I know in the past I have removed a proximal embolus only without suspecting at the time the presence of distal emboli, because even in such circumstances there is some retrograde flow from the distal end of the arteriotomy wound. Nowadays distal emboli are always presumed.

I am certain it is because emboli are rarely single that the results of surgery have been so discouraging.

Before this appreciation of the morbid anatomy of peripheral embolism, my results conformed with the majority. Of the 38 cases recorded above 10 were referred to surgery. 5 subsequently suffered amputation, 2 recovered with impaired circulation and only 3 with a normal circulation. These 3 complete successes were all operated on within six or at most eight hours after symptoms occurred. After operations on the heart and major vessels, clot from the site of operation may escape and lodge distally and its removal at the end of the operation is nearly always successful with return of normal circulation. Early operation for embolism is therefore important, and there is no reason for waiting an hour or two to see what is going to happen, and I am not convinced that adequate doses of heparin will prevent consecutive thrombosis and, if cure rather than limb survival is the aim, removal is essential so that a wait-and-see policy is completely unjustified.

TABLE I.—TOTAL NUMBER OF OPERATIONS BEFORE 1958

	Number	Success	Limb survival	Amputation or death
Aortic ..	5	1	2	2
Iliac ..	2	1	—	1
Femoral ..	6	3	1	2
Popliteal ..	2	1	—	1
Axillary ..	2	2	—	—

plus 7 successes out of 8 immediately after major vessel surgery.

One of the major technical difficulties in embolectomy has been getting the clot out of the vessel, and in discussing this Olwin *et al.* (1953) suggested the simple method of retrograde flushing with saline through a cannula inserted into the posterior tibial artery. Flushing has to be as forceful as possible, and I find this is best done with a 300 ml. bladder syringe; at first the importance of force, especially in long-standing cases, was not appreciated and we were not impressed with the method. It is often better to wash out the vessel in segments unless the operation is done very early. The use of forceful retrograde flushing has completely revolutionized the treatment of peripheral emboli. Not only is the vessel cleared without any doubt at all, but if there is any spasm associated with embolism, this is forcibly overcome and is certainly not apparent at the end of the operation, pulses returning immediately. Furthermore, this operation has been done in late cases, up to four days in one, and three in another, with complete success (Fig. 1). If, given restoration of the circulation, recovery of the limb is possible, time does not seem to matter much. It seems that multiplicity of the intravascular clots is of greater importance than intimal damage.

FIG. 1.—Clot removed from the iliac, femoral and popliteal arteries of a 78-year-old female patient. The circulation was restored and distal pulses remain patent.

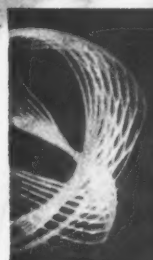
The operation of forceful retrograde flushing has been done eight times now with complete restoration of blood flow in 7, and it is advised even at a late stage if the limb is viable. In one patient aged 72 years with a forty-eight-hour embolism, though gangrene was averted and pulses are now present, muscular power is very poor as much muscle is dead, but he can walk.

In a patient with marked atherosclerosis where emboli obstruct the aortic bifurcation, the iliac or possibly the femoral artery, it would seem proper to remove the embolus and to do an endarterectomy at the same time. The two occasions on which this has been done were successful.

The rather hopeless attitude towards peripheral embolism should be replaced by an aggressive one. First, the term "limb survival rate" should be abandoned and the word "cure" reinstated. Secondly, embolectomy by forceful retrograde flushing should be done at the earliest possible moment, but even if the patient is seen late and the limb is in jeopardy though still viable, it should still be done. Thirdly, serious consideration should be given to atrial appendicectomy with or without mitral valvotomy at the time of, or very shortly after, the first embolectomy.

REFERENCE

OLWIN, J. H., DYE, W. S., and JULIAN, O. C. (1953) *Arch. Surg., Chicago*, **66**, 480.



VASCULIT

a haemokinetic agent

for increased peripheral blood flow

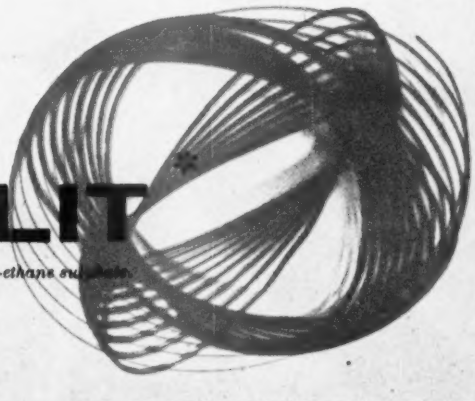
Recently introduced to the Medical Profession in this country, Vasculit is a haemokinetic agent which produces a marked increase in peripheral blood flow. This is accompanied by an increase in cardiac efficiency associated with an increase in stroke volume The heart rate remains unchanged.

In therapeutic dosage, the action of Vasculit is immediate and free from the common and often intense side-effects associated with conventional treatment of deficient peripheral blood flow. Clinical investigations reveal no significant fall in blood pressure and no extrasystoles or other arrhythmias have been observed. Apart from its therapeutic effects, Vasculit is reported to create a subjective feeling of well-being.

Vasculit is available both in drop and tablet form. This permits precise and flexible dosage to suit the varying needs of individual patients.

Good results have been obtained with Vasculit in the treatment of many vasomotor disorders, delayed union of fractures, in traumatic osteoporosis and in bedsores[1]. It has also been used with benefit in post-thrombotic conditions[2] and has received numerous favourable reports as a valuable adjuvant in the treatment of indolent ulcers of the leg[3]. Headaches and cerebral symptoms associated with essential hypertension and arteriosclerosis have been promptly relieved[4].

1. *Arch. Orthop. Unfallchir*, (1956) 48, 209.
2. *Wien. Klin. Wschr.* (1954) 66, 743.
3. *Hautarzt*, (1953) 4, 78.
4. *Wien med. Wschr.* (1951) 101, 544.



VASCULIT

1-(4-hydroxyphenyl)-1-hydroxy-2-n-butylamino-ethane sulphate.

** Regd. Trade Mark*

Manufactured and distributed in the U.K. by Pfizer Ltd., Folkestone, Kent, for
C. H. BOEHRINGER SOHN, INGELHEIM AM RHEIN
Registered proprietors of the Trade Mark

When anxiety

adds to her problems

It may be the exaggeration of a teenage tension or may be just the embarrassment of the spots and pimples of adolescence; it may be premenstrual irritation or menopausal misery—whatever the issues that cloud her emotional judgement, Equanil will help your patient to view her life without the accompaniments of anxiety, worry and tension.

Equanil is the safe, selective sedative—it relaxes both mind and muscle.

Equanil

MEPROBAMATE

Available as 400 mg. tablets. Bottles of 20 and 250.
Equanil H.S. 200 mg. tablets. Tubes of 20 and bottles of 250.

*trade mark

Write for detailed information

JOHN WYETH & BROTHER LIMITED, CLIFTON HOUSE, EUSTON ROAD, LONDON, N.W.1

Eql. 12c

Section of Surgery

President—ROBERT COOKE, Ch.M.

Meeting
October 1, 1958

DISCUSSION ON PRESENT-DAY VIEWS ON THE TREATMENT OF THYROID CONDITIONS (OTHER THAN CANCER)

Dr. B. Marden Black (Mayo Clinic and Mayo Foundation,[1] Rochester, Minnesota, U.S.A.):

Treatment of Benign Goitres

Until some fifteen years ago, thyroidectomy was the only definitive treatment of practically all types of goitre. The discovery of antithyroid drugs in 1943 and the availability of radioiodine a few years later provided two additional methods of treating thyrotoxicosis. More recently, medical methods of treating Hashimoto's disease and granulomatous thyroiditis have been found. The use of conservative methods of treatment, in which tissue is not available for microscopic examination, has stimulated an increased interest in the incidence of clinically unrecognizable, or so-called occult, carcinoma. It is not surprising, in view of these and other relatively recent developments, that there are still uncertainty and some disagreement over the preferred method of treatment of the various thyroid states.

NON-TOXIC NODULAR GOITRE

The advisability of removing large non-toxic nodular goitres for cosmetic reasons, to relieve pressure effects, or prophylactically to prevent the development of thyrotoxicosis is generally accepted. With smaller goitres, when the traditional indications for thyroidectomy are absent, the sole reason for advising thyroidectomy is the possible presence of an occult carcinoma.

The incidence of clinically undetectable carcinomas in non-toxic nodular goitres which have been removed surgically has been studied repeatedly (Cole *et al.*, 1945; Piercy, 1956). In the majority of studies an incidence of 4% to 8% has been found, although extremes of from less than 2% to as high as 17% have been reported. The findings of Beahrs *et al.* (1951) in a series of more than 3,000 cases of nodular goitre in euthyroid patients were in keeping with the majority. Among cases in which there was no indication in the patient's record of any suspicion of cancer, apart from the presence of a nodule or nodules within the thyroid, the incidence of cancer proved to be 3·8%. When pre-operative clinical impression was disregarded, the proportion in which cancer was found rose to 7·5%.

Our findings were practically identical to those of Mortensen *et al.* (1954) in a series of 1,000 consecutive necropsy cases at the Mayo Clinic. After removal, the thyroid glands were studied as is done customarily in the laboratory of surgical pathology. Grossly visible nodules were present in 525 of the thyroids, and occult cancers were found in 26 (5%). The incidence of cancer in solitary nodular goitres was approximately twice as great.

The two series from the Mayo Clinic together with other reports suggest that a reasonable estimate of the incidence of occult cancer in non-toxic nodular goitre is approximately 5%. There is general agreement that the incidence of cancer is greater in men than in women with nodular goitre, and that it is materially greater in younger than in older persons. In children 14 years of age or less, cancer is present in more than one-third of all nodular goitres (Hayles *et al.*, 1956).

In addition to such statistical considerations, the clinical behaviour of occult carcinoma has some bearing on whether thyroidectomy should be advised. For the most part the lesions are small papillary adenocarcinomas that have neither extended locally beyond the capsule of the thyroid nor metastasized. The progress of such lesions is so slow that years may pass before they become evident clinically, and an even longer interval before they produce symptoms. It is quite likely that older patients and those with decreased expectancy would live out their lives before the lesion caused difficulties. This is well demonstrated in the review of necropsy cases mentioned previously. Although the solution of the problem of the small nodular goitre is far from satisfactory, it would seem that, in general, unless local findings suggesting carcinoma are present, the goitre can probably be observed with safety to the patient in persons beyond middle age, particularly in women with multiple nodules in the thyroid. Conversely, thyroidectomy is advisable in younger persons, in men, and when the nodules are solitary.

Uptake of radioiodine.—Of the presently available tests, only one has any importance in

[1]The Mayo Foundation, Rochester, Minnesota, is a part of the Graduate School of the University of Minnesota.

differentiating benign from malignant nodules. After a tracer dose of radioiodine, differences in regional uptake in the thyroid may be detected by mechanical scanning devices. Since carcinomas practically never trap iodide as effectively as does benign thyroidal tissue, increased uptake in a nodule provides strong evidence that the nodule is not malignant. Decreased uptake or no uptake does not imply that the nodule is malignant however, since many adenomas do not trap iodine. In practice, a surprisingly large number of adenomas in euthyroid patients have been found to trap more iodide than the remainder of the thyroid. Since a hyperfunctioning nodule might well lead in time to clinical hyperthyroidism, the presence of such a nodule is coming to be regarded as an indication for thyroidectomy. Thus, the use of the test is possibly increasing the number of patients thought to require surgical treatment.

Adenomatous Goitre with Hyperthyroidism

Because of the hyperthyroidism, treatment is of course mandatory, and subtotal thyroidectomy is overwhelmingly the treatment of choice. Antithyroid drugs, regardless of dosage, are relatively ineffective in controlling the hypermetabolism, so that treatment for many months is usually necessary before the patient becomes euthyroid. The continued period of hyperthyroidism is always harmful, and may not be tolerated by a seriously ill patient. Adenomatous goitre with hyperthyroidism is treated with radioiodine far less satisfactorily than is exophthalmic goitre for several reasons. Uptake of iodide, and hence radiation effects, are spotty. It is impossible to judge the weight of the hyperfunctioning tissue clinically; indeed, even the size of large goitres, particularly those with substernal extension, can be estimated only crudely. The hyperplastic tissue of exophthalmic goitre is apparently reasonably radiosensitive while that of adenomatous goitre, by comparison, is radioresistant. The mere size of the goitre, regardless of uptake, which is usually not great, implies large or perhaps excessive amounts of radioiodine for treatment. Finally, radioiodine does not rid the patient of the goitre.

Rarely, patients with toxic nodular goitres are so ill that the risk of thyroidectomy is prohibitive. In such cases, treatment with radioiodine is preferable to that with antithyroid drugs. In spite of its disadvantages compared to thyroidectomy, treatment with massive dosage of radioiodine is occasionally successful. After recovery of the patient, thyroidectomy may or may not be advisable, depending largely on the life expectancy of the patient and the presence or absence of pressure effects.

Exophthalmic Goitre

There has been an adequate opportunity during the past decade to assess the merits of the three methods of treating exophthalmic goitre now available. As definitive treatment, it would appear at present that the antithyroid drugs are being abandoned, and that radioiodine is increasingly replacing subtotal thyroidectomy.

Antithyroid drugs or goitrogens.—The early enthusiasm over the use of antithyroid drugs was tempered somewhat by the frequency of drug reactions, particularly of neutropenia and agranulocytosis. Safer drugs were developed promptly so that drug reactions ceased to be a major problem. It soon became evident, however, that the drugs were merely suppressive, and that the hypermetabolism recurred promptly on cessation of treatment. Furthermore, since the intensity of exophthalmic goitre varies from time to time, it is necessary to adjust the dosage occasionally to ensure continued control. This, together with the occasional development of drug reactions, requires continued medical observation until the disease has run its course, often for as long as two to three years. In practice, definitive treatment with antithyroid drugs has proved so unsatisfactory that it is rarely attempted. The few remaining advocates of the treatment still hold that milder disturbances, particularly those in which the thyroid is small, may be so managed successfully. There are also those who prefer to control exophthalmic goitre in children with antithyroid drugs.

There is currently more interest in the use of antithyroid drugs to prepare patients for thyroidectomy. It is argued that euthyroid patients may be treated more safely surgically than may hyperthyroid patients. It is not difficult to suppress the hypermetabolism or to maintain the metabolic rate in the euthyroid range for a few weeks or months. The antithyroid drug is given in sufficient dosage to reduce the basal metabolic rate to normal. Some three weeks before the anticipated time of thyroidectomy, iodide therapy is begun and a week later the treatment with antithyroid drugs is stopped. Another common practice is to begin giving iodides when the basal metabolic rate has fallen to perhaps +20%, and to carry out the thyroidectomy two to three weeks later.

The group at the Mayo Clinic, along with many others, has not adopted this plan of preparation as a routine. We have believed for years that in the case of usual intensity thyroidectomy, after adequate preparation with iodides, can be carried out without increased risk. Consequently, the time and effort necessary for preparation with antithyroid drugs would seem unnecessary. We see no particular reason to change our practice,

particularly since we have had no post-operative deaths among our patients after thyroidectomy for exophthalmic goitre since 1946.

I feel that patients with unusually severe disease, either because of the intensity of the thyrotoxicosis or because of visceral damage, should be prepared with antithyroid drugs. In such serious cases, after the patient has become euthyroid, medical control is continued until the patient has recovered from the effects of the thyrotoxicosis. Medical control might well be continued advantageously for several months. Iodides should be given for a sufficient time before thyroidectomy to produce involution of the thyroid; this can be determined easily by palpation. In actual practice, the need for preparation with antithyroid drugs rarely arises since most patients with exophthalmic goitre of this severity may be treated more advantageously with radioiodine.

Radioiodine.—In the treatment of exophthalmic goitre, destruction of the thyroid with radioiodine is as effective as surgical removal. Pre-operative preparation, the surgical procedure, hospital care, and a period of convalescence are all avoided. The cost in terms of both time and money is far less than that of thyroidectomy. The hypermetabolism declines somewhat more slowly than after thyroidectomy, a point of little practical importance; however, the surviving parenchymal and stromal cells of the thyroid as well as the hæmatopoietic tissues are exposed to ionizing radiation, a matter that may be of considerable practical significance. At the dose levels employed there are no immediate effects of irradiation. The only complication that has been observed as yet is the development of myxœdema. After large doses, given with the idea of inducing a remission with one treatment, myxœdema develops in about one-third of the cases. The number of cases in which myxœdema develops can be reduced probably to that which ensues after thyroidectomy if several smaller doses are employed. In any event the complication is not serious and can be managed easily.

The one deterrent to the use of radioiodine is fear of delayed carcinogenic effects of the ionizing radiation in the thyroid or blood-forming tissues. Treatment with radioiodine has now been employed extensively for more than ten years, and no acceptable case of malignant disease resulting from the irradiation has yet been reported. While this is reassuring, at least another five or possibly ten years will be necessary before the matter can be resolved.

Meanwhile it would seem prudent to limit treatment with radioiodine to older patients and to those with decreased life expectancy. My colleagues and I for the past few years have regarded radioiodine therapy as the treatment of choice for patients 45 years of age or older, and for younger patients with associated diseases which decrease their life expectancy. It is also employed occasionally in younger persons with recurrent exophthalmic goitre, particularly when complications such as injury to one recurrent laryngeal nerve or perhaps transient tetany occurred after the previous thyroidectomy. Because of possible genetic effects, radioiodine is contra-indicated in women of child-bearing age. The thyroid of the human fœtus traps iodine after the first trimester of pregnancy. This should be recalled if for any reason radioiodine is employed during pregnancy.

Subtotal thyroidectomy.—After suitable preparation with iodides, or, as discussed previously, with antithyroid drugs and iodides, subtotal thyroidectomy is an extremely safe and effective method of treatment. It remains the treatment of choice for persons less than 45 years of age, and occasionally for older patients with unusually large goitres and for those with an abnormally low uptake of radioiodine. Currently at the Mayo Clinic between 30% and 40% of patients with exophthalmic goitre are being treated surgically while the remainder are receiving radioiodine.

Other Diseases

Colloid goitre.—Except in regions of endemic goitre, colloid goitres large enough to require treatment are unusual. The traditional treatment is with desiccated thyroid, iodides, or more commonly both. If nodules persist or appear as the size of the goitre decreases, thyroidectomy should be considered.

Hashimoto's thyroiditis.—The recent work, particularly of Rose and Witebsky (1956), Doniach and Roitt (1957) and of others, has demonstrated that Hashimoto's thyroiditis is the result of an auto-immune reaction to the patient's own thyroglobulin. The plasma cells and lymphocytes in the thyroid and the regional lymphadenopathy are the result of the antigen-antibody reaction locally. Immune globulins are increased in the serum, and also present may be an abnormal protein-bound-iodine complex which is probably thyroglobulin. The oxyphilic hyperplasia of the parenchymal thyroid cells presumably results from increased levels of thyrotrophin, which in turn results from failure of the damaged thyroid to produce normal amounts of metabolic hormones. The entire process should be terminable by giving desiccated thyroid or triiodothyronine. One of the first series of patients treated successfully by means of thyroid was that of Furr and Crile in 1954. They reported the successful reduction in size of the goitre in 12 cases. It is of some interest that in

one case the goitre recurred after treatment was stopped.

McConahey *et al.* (1959) have recently reported our experience in the treatment of approximately 100 patients. The diagnosis in about half of the cases was established by means of needle biopsy, whereas it was made clinically in the remainder. The response to treatment was usually slow, often requiring three to six months or even longer. In about half of the cases, the goitre disappeared entirely, while in the others there was some reduction in the size of the gland. With few exceptions, the rapidity and degree of the reduction in size of the goitre could be correlated with the presence of fibrosis. Reduction in size of hard, fibrous glands was not striking and was usually slow, while that of softer goitres with little fibrosis was far more rapid and striking.

It would appear that treatment with thyroid is practical and preferable to thyroidectomy, except possibly in rare cases in which the goitre is huge and is causing pressure symptoms. The diagnosis should be established with certainty, and needle biopsy of the thyroid is at present a more direct and surer method than tests based on changes in the metabolism of iodine or than immunologic tests.

Needle biopsy of the thyroid seems to be both safe and practical, provided the thyroid is large enough to permit a reasonable insertion of the cutting part of the device. The only other difficulty encountered has been the securing of an adequate biopsy specimen from extremely fibrous thyroids. The sole complication observed in more than 150 cases in which needle biopsy had been carried out was hæmorrhage in an adenoma in one case of adenomatous goitre.

Acute diffuse thyroiditis. — Acute diffuse thyroiditis, or granulomatous thyroiditis, is a viral disease in which there may be escape of thyroglobulin from follicles, giving rise to the same changes that occur in Hashimoto's thyroiditis. This probably explains the somewhat limited success of treatment with antithyroid drugs which were formerly employed. It has also been known for many years that irradiation would hasten the course of the process. The present treatment of choice is by means of steroid hormones. The response to steroid therapy is dramatic and complete although purely symptomatic. Treatment must be continued with the least amount of drug necessary to control symptoms until the disease has run its course.

Riedel's thyroiditis.—Riedel's thyroiditis is one of the least common diseases of the thyroid. The massive fibrosis extending beyond the capsule of the thyroid to involve neighbouring structures is indistinguishable clinically from advanced, locally inoperable carcinoma. Surgical exploration is necessary to establish the diagnosis and to free the trachea and œsophagus from the compressing fibrous mass. Thyroidectomy and resection of extrathyroidal fibrous tissue are usually impossible and should rarely be attempted.

SUMMARY

In general, small non-toxic adenomatous goitres should be removed because of the possible presence of an occult carcinoma. In older persons, particularly with multiple soft nodules, the goitre may be left alone with reasonable safety. Large non-toxic nodular goitres should be removed. The treatment of choice of nodular goitre with hyperthyroidism is thyroidectomy. Exophthalmic goitre may be treated by antithyroid drugs, radioiodine or thyroidectomy. The antithyroid drugs are rarely used at present as definitive treatment, but they have some value in pre-operative preparation. Radioiodide is the agent of choice in older persons, while thyroidectomy is indicated in younger persons, particularly in women of child-bearing age and during pregnancy. Hashimoto's thyroiditis and colloid goitre should be treated with desiccated thyroid, granulomatous thyroiditis with adrenal steroids, and Riedel's thyroiditis by means of "partial" thyroidectomy.

REFERENCES

BEAHRS, O. H., PEMBERTON, J. DEJ., and BLACK, B. M. (1951) *J. clin. Endocrin.*, **11**, 1157.
COLE, W. H., SLAUGHTER, D. P., and ROSSITER, L. J. (1945) *J. Amer. med. Ass.*, **127**, 883.
DONIACH, D., and ROITT, I. M. (1957) *J. clin. Endocrin.*, **17**, 1293.
FURR, W. E., Jr., and CRILE, G., Jr. (1954) *J. clin. Endocrin.*, **14**, 79.
HAYLES, A. B., KENNEDY, R. L. J., WOOLNER, L. B., and BLACK, B. M. (1956) *J. clin. Endocrin.*, **16**, 1580.
MCCONAHEY, W. M., WOOLNER, L. B., BLACK, B. M., and KEATING, F. R., Jr. (1959) *J. clin. Endocrin.* (In press.)
MORTENSEN, J. D., BENNETT, W. A., and WOOLNER, L. B. (1954) *Amer. Coll. Surg., surg. Forum*, **5**, 659.
PIERCY, J. E. (1956) *Proc. R. Soc. Med.*, **49**, 174.
ROSE, N. R., and WITEBSKY, E. (1956) *J. Immunol.*, **76**, 417.

Mr. Rupert Vaughan Hudson (London):

Treatment of thyroid disease cannot be commenced until the diagnosis is established. On the presentation of the patient a full clinical examination is made and the patient is tentatively allocated into one of the following groups according to:

(1) Whether the goitre is diffuse or nodular.

(2) The presence or absence of thyrotoxicosis in normal or abnormal rhythm.

(3) The evidence of pressure on the great veins, trachea, or recurrent laryngeal nerve.

(4) Whether clinically the condition is benign or suspicious of malignant change.
(5) The possibility of the association of thyroiditis or lymphadenoid goitre.
(6) The presence or absence of exophthalmos.
(7) Pregnancy.

The following laboratory tests are performed as a routine in all thyroid patients: the basal metabolic rate; the radioactive iodine twenty-four-hour uptake and excretion; the topographical survey of the gland; the forty-eight-hour plasma radioactivity and protein-bound fraction. We make use of the Werner ^{131}I suppression test using triiodothyronine when thyrotoxicosis is in doubt, or in the case of "hot" nodules. More recently we have used as a routine three serological tests: (1) complement-fixation, (2) tanned red cell test, (3) precipitin test.

A diagnostic X-ray of the trachea and thoracic inlet is performed as a routine.

We would like to do the serum protein flocculation tests as a routine, namely, the thymol turbidity, zinc sulphate turbidity, and the colloidal gold, but, because of the pressure of work upon the laboratories, we only make use of them in cases where auto-immunity is suspected.

We find the basal metabolic rate still of the greatest value as a measure of the patient's overall hormone balance, and particularly in the detection of early and incipient myxœdema. In the detection of mild cases of thyrotoxicosis the assistance of radioactive isotopes is of more help, but both tests have the greatest value when used concurrently.

Serological Tests

There are two thyroid antigens which can give rise to auto-antibodies, one represented by the complement-fixation, and the other by the tanned red cell test. The former has been localized to the "microsome" fraction of actively secreting thyroid cells; the latter to thyroglobulin itself, and this bears a close relation to the precipitin reaction. The complement fixation can be present in some patients therefore in the absence of thyroglobulin antibodies.

We are still trying to evaluate our serological tests, and up to the present time the views of Dr. I. M. Roitt, Dr. Deborah Doniach and myself are as follows:

(1) The higher the immunity the more probable is a greater lymphadenoid invasion of the thyroid gland and strongly positive complement-fixation, tanned red cell and precipitin tests.
(2) An intermediate group where the serological tests are of moderate intensity possibly indicating a moderate or low degree of lymphadenoid change in the gland.
(3) Where the levels of antibody are low, or if none can be detected there may occasionally still be histological proof of a minor lymphadenoid change.

On the whole the tanned red cell test is the most delicate and the least significant in prognosis when its presence can only be detected at low level. At high level it is diagnostic of a high degree of lymphadenoid infiltration. With regard to the complement-fixation test a positive finding in minor degrees of lymphadenoid infiltration is about half as common as that of the tanned red cell test, but when an advanced stage of auto-immunity is reached the complement-fixing antibody is present together with the thyroglobulin antibody in the majority of patients.

We find the presence of an antibody is relatively common in all thyroid diseases. For instance in 181 toxic diffuse goitres two-thirds have a very low or moderate level of antibody which is only detected by the tanned red cell or complement-fixation, or both, but 1–2% of patients have a high level, and we believe that these may develop myxœdema in the course of time either spontaneously or following thyroidectomy; even patients with moderate or low levels may eventually become myxœdematous.

In non-toxic nodular goitre, however, the percentage of positive antibody tests is relatively low, but here also there are 1–2% with a high level and who may be passing on to Hashimoto's disease.

Diffuse Non-toxic Goitre

We rarely see the diffuse goitre at puberty in the surgical clinic, but a certain number of cases between the ages of 20 or 30, or in the later age groups. It is in these patients that we are constantly on the look-out for the possibility of lymphadenoid change. These patients whom we have proved to our satisfaction to have a marked lymphadenoid change can be divided into four groups: (1) Lymphadenoid goitre and thyrotoxicosis. (2) Euthyroidism. (3) A moderate degree of hypothyroidism. (4) Frank myxœdema.

The gland may be of any size, it may be small, moderate or large, it is always firm, it is more usually symmetrical but a change may be greater in one lobe than another; not infrequently the pyramidal lobe is palpable, often the surface of the gland is uneven and may, as Joll (1939) stated, be bosselated; this may be so marked that it is difficult clinically to say whether it is a nodular goitre or not. Occasionally large cervical nodes are present and this adds to our difficulty in diagnosis.

Patients may complain of irregular attacks of pain in one or other lobe, the pain may be referred to the corresponding auditory meatus, and the gland may be tender on palpation. The gland moves well on swallowing but may not be readily movable, and if this is accompanied by fibrosis will be very hard, and there is particularly also then a tendency to narrowing of the trachea, even with stridor.

We feel confident in the presence of such physical findings, a raised E.S.R., positive flocculation tests, a uniform radioactive iodine topography and a normal or raised uptake, together with positive precipitin, tanned red cell and complement-fixation tests, that we are dealing with an extensive lymphadenoid goitre or Hashimoto's disease.

Toxic Hashimoto's disease is treated with carbimazole, and the *non-toxic* cases with thyroid extract. The average dose is 2 grains of thyroid extract daily; a larger dose may be tolerated but in some it gives rise to symptoms of overdosage.

We are fully aware that carcinoma, reticulum cell sarcoma, and lymphosarcoma can be associated with Hashimoto's disease.

To summarize, with all these tests positive there is a high degree of immunity, a relatively extensive lymphadenoid change, and a strong possibility of progress towards myxœdema, if myxœdema is not already present. On the other hand all cases do not progress to myxœdema and may remain as it were in balance. For instance we have seen a patient with marked infiltration of lymphadenoid tissue in a thyrotoxic gland who remained euthyroid and perfectly well for twenty years after surgery and then suddenly developed marked recurrent hyperthyroidism with enlargement of the remnants. Dunhill (1937) in his Lettsomian Lectures reported a similar case. Raymond Greene (1957) has also commented upon this.

Virus thyroiditis (De Quervain's disease).—Our experience with this is small but there may be:

(1) The absence of thyroid auto-antibodies and resolution of the disease.

(2) The appearance six to eight weeks after the inception of the disease of auto-antibodies of low titre followed by their disappearance and resolution of the disease.

(3) The presence of positive serological tests which increase and the gradual progress of the disease to true Hashimoto and towards myxœdema.

An example of such a case has now been recorded in the Belgian literature (Druez *et al.*, 1958).

Spontaneous or medical myxœdema.—We have now tested the sera of 100 cases, and we have evidence that in 82% of primary myxœdema occurring in middle age, the hormonal failure was preceded by a lymphadenoid change and the small goitre has insidiously progressed to atrophy with absolute myxœdema.

Results of treatment of Hashimoto's disease.—In these proven cases thyroid extract will lead to diminution in the size of the gland, improvement in well-being, and the opening up of the narrowed trachea. During the process of resolution the gland softens and becomes smaller and may disappear. A small proportion maintain a soft small goitre and in a few the goitre is smaller but remains very firm.

Non-toxic Nodular Goitre of Relatively Small Size

The hard core of our work is the attempt to decide whether a single nodule, or one of a multinodular goitre, is pre-cancerous or cancerous. Like Raymond Greene (1957) and many others we have for a considerable time made use of the topographical survey of radioactive iodine uptake over the thyroid area and attempted to divide the nodules into "hot", "neutral" and "cold".

In the absence of pressure, and if we think that malignant disease can be excluded, particularly in young patients, we treat these patients expectantly either with thyroid extract, triiodothyronine or triiodothyroacetic acid, in physiological dosage; there appears to be little difference in these three methods. All we can hope to do is to prevent enlargement of the thyroid and postpone thyroidectomy. In 10–15% there is a substantial reduction in the size of the goitre. Unfortunately we cannot as yet predict which goitre will respond to this medical treatment, but we think that it is well worth a trial.

We are conscious of the fact that if a suspected pre-carcinomatous or carcinomatous lesion is found at the time of surgery to be innocent, and many small concealed nodules are also found to be present in the gland, a relatively radical operation will have to be performed to prevent an early recurrence. A proportion of these patients will have to be maintained on thyroid medication, and probably for life, but it is surprising that a very small remnant is compatible with euthyroidism for a long period of time. We are also conscious of the fact that a malignant recurrence can, after a period of time, follow the surgery of a benign goitre. It is possible that the persistent stimulation by T.S.H. can convert a benign remnant to a malignant recurrence.

In spite of these statements, we are very conscious that it is a disaster not to remove a pre-carcinomatous or carcinomatous lesion, for if they are well encapsulated the results are extremely good if an adequate thyroidectomy is per-

formed. Therefore, if a non-active single nodule is present, or if there is a doubt as to a portion of a multi-nodular goitre, the whole gland is exposed and dealt with accordingly.

Non-toxic nodular goitres of sufficient size to cause pressure are a different matter and are dealt with by surgery. If an adequate operation is performed many will need the assistance of thyroid extract.

Toxic nodular goitres, whether accompanied by arrhythmia or normal rhythm, are also treated by surgery.

Diffuse toxic goitres in abnormal rhythm are treated by surgery. In this respect we found, after a very long follow-up, that there is one group, and this applies also to toxic goitre in normal rhythm, which is liable to recur, and these are patients with a very small hard adherent vascular thyroid gland.

It is probable that these patients are better treated initially by adequate radioactive iodine therapy if they are aged over 40.

Toxic diffuse goitres in normal rhythm are usually sent to the clinic because of the failure of antithyroid drug treatment, or because the patients themselves refuse to continue with this treatment. These are treated by surgery. Patients sent initially and without treatment to the clinic are given a trial of antithyroid drug therapy and we have found carbimazole most satisfactory. In a five-year follow up 50% remain in remission on completion of treatment, but we are unable to state whether some of these will relapse in years to come. The failures are treated by surgery.

Radioactive iodine.—We are very conservative in the use of radioactive iodine, using it as an initial form of treatment in diffuse goitre when there is an expectation of life of not more than twenty years. We use it at an earlier age, however, or at any age, for recurrence of thyrotoxicosis with or without normal rhythm when the remnants are small, and particularly where there is already a palsy of one or other recurrent laryngeal nerve. A recurrent nerve palsy usually means the loss of one or more parathyroids owing to damage of the posterior border of the gland. Further surgery, therefore, increases the risk of morbidity and an adequate safe surgical removal may be extremely difficult.

Exophthalmos and toxic goitre.—In 50% exophthalmos of major or moderate degree accompanies the thyrotoxicosis. The prognosis is twofold, one for the eyes and the other for the thyrotoxicosis. We have adopted the principle of first dealing with the thyrotoxicosis by an adequate surgical removal even at the risk of myxœdema, and carefully correcting this with the use of thyroid extract. 99% improve or show a complete resolution following surgery. 50% of those with early ophthalmoplegia recover, and two-thirds of those with a marked threat of progressive exophthalmos also recover. Lateral tarsorrhaphy and radiotherapy to the orbits, as advocated by Jones (1951), may be necessary as an adjunct to surgery.

In my figures the male is more prone to exophthalmos, and four and a half times more liable to ocular complications than the female. Russell Brain (1945) has already pointed this out.

Pregnancy.—It is a personal view that surgery should be avoided during pregnancy. It is very common to find that thyrotoxicosis spontaneously lessens after the fourth month of pregnancy and thereafter improves. Small doses of carbimazole may be necessary. This treatment is perfectly safe for the fœtus provided the mother is not over-dosed with the drug. It is requested that the child is not breast-fed for it is during lactation, particularly if this is prolonged, that the gland commences to enlarge and the thyrotoxicosis flares again. Six months after pregnancy the whole position is reassessed.

Children.—Children should be treated, if possible, by antithyroid drugs until puberty is well established. Subsequently surgery may be necessary.

Obesity.—It is interesting to find that many patients have passed through a period of excessive weight at some time in their life. In some cases thyrotoxicosis even when severe can be accompanied by increase in weight, and these patients form a particular post-operative problem.

Associated lesions.—Time prevents mention of the effects of thyroidectomy upon associated lesions, for instance, hypertension, rheumatoid arthritis, tuberculosis, gastric and duodenal ulcer, and diabetes.

As a surgeon I would like to ask what should be done about the prophylaxis of goitre? What is the correct treatment for puberty goitre, and have members personally seen a patient with a normal radioactive iodine turn-over, no evidence of past or present thyrotoxicosis and progressive exophthalmos.

REFERENCES

BRAIN, W. R. (1945) *Proc. R. Soc. Med.*, **38**, 666.
DRUEZ, G., HAUT, J., PARMENTIER, R., and MUSIN, L. (1950) *Acta clin. belg.*, **13**, 280.
DUNHILL, T. P. (1937) *Trans. med. Soc., Lond.*, **60**, 2462.
GREENE, R. (1957) *Ann. R. Coll. Surg. Engl.*, **21**, 73.
JOLL, C. A. (1939) *Brit. J. Surg.*, **27**, 351.
JONES, A. (1951) *Brit. J. Radiol.*, **24**, 637.

Professor Russell Fraser supported Mr. Vaughan Hudson's comment that there was still a place for antithyroid drug therapy in thyrotoxicosis, especially in pregnancy and in young

patients, but also in any patient under 45 not keen on surgery. At five years after stopping this prolonged treatment, he had found a remission rate of about 60%, but did not use this treatment with patients who had a large or nodular goitre. He also emphasized the importance during and after any antithyroid therapy (whether operative or by drugs) of the administration of thyroid in cases with moderate or severe exophthalmos to prevent any worsening of this. The dosage should be equivalent to 3–6 grains of thyroid a day. Unfortunately this could not treat the condition but prevented it being worsened by these treatments.

Another new development in thyroid diagnosis was the needle biopsy, and this was of increasing help, especially now that the lymphadenoid goitre was so much more often suspected in apparent non-toxic goitres.

Mr. Selwyn Taylor said that Dr. Marden Black had made a strong case for the pre-operative treatment of the toxic thyroid with iodine and Professor Russell Fraser had been equally eloquent in recommending the antithyroid drugs. It seemed to Mr. Taylor that geographical reasons determined which was used. Where patients came from a distance, as they all did at the Mayo Clinic, they required rapid stabilization and treatment which Lugol's solution followed by thyroidectomy provided. If patients lived near their place of treatment, as was usual in this country, a much longer-term policy could be entertained and thyroidectomy was then only an incident in the management of a patient who was already euthyroid.

Miss G. Barry said that paradoxically, being a surgeon, she was in favour of treating primary thyrotoxicosis in young people medically by antithyroid drugs. She had seen many young women put on too much weight after a partial thyroidectomy, and they had had to spend the rest of their miserable lives on a strict reducing diet—feeling guilty every time they had a good meal; they could not be given thyroid extract because they might rapidly develop tachycardia again. There was no reason why a young patient should not stay on carbimazole therapy for long periods of time. It was well tolerated; it was easy to vary the dose as the severity of the symptoms altered. In fact she never operated on these young people unless forced to by her medical colleagues.

Meeting
November 5, 1958

Amyloid Disease of the Thyroid.—P. J. W. Monks, F.R.C.S. (for Professor R. Milnes Walker, M.S., F.R.C.S.)

Mrs. P. B., aged 79, with long-standing bronchiectasis, developed a hard diffuse goitre over two years. This caused considerable anteroposterior tracheal compression. Subtotal thyroidectomy was performed in September 1957 and a moderate sized (208 grams) firm, pale goitre, encircling the trachea and œsophagus, was removed. Histological examination showed the parenchyma represented by a few thin-walled acini containing poorly staining colloid. The interstitial tissue was hyaline and gave a strongly positive methyl violet stain for amyloid.

In October 1958 no further evidence of amyloid disease had developed; clinical examination, the urine and the Congo red test were normal. Her general health had improved.

Comment.—About 60 cases of amyloid disease of the thyroid have been reported (Rundle, 1951). Most of these have been associated with widespread amyloidosis and in only half has there been a well-marked goitre. Walker (1942) could find only two cases with the disease localized to the thyroid.

The diagnosis should be considered when a diffuse firm goitre develops fairly quickly during the course of an illness likely to cause amyloidosis. The gland enlarges uniformly, is firm and tends to cause obstruction. Myxœdema has not been reported. The diagnosis is normally confused with malignancy or Hashimoto's disease.

Rundle (1951) advised against thyroidectomy, but if tracheal obstruction is present and the disease is apparently localized operative treatment is clearly indicated.

REFERENCES

Rundle, F. F. (1951) Joll's Disease of the Thyroid Gland. 2nd ed. London.
Walker, G. A. (1942) *Surg. Gynec. Obstet.*, **75**, 374.

Sarcoidosis of Thyroid.—Robert Cooke, Ch.M.

In January 1956 a woman of 56 years presented with a large thyroid swelling, which was giving rise to dyspnœa on exertion and, what was much more unusual, dysphagia.

There was a history of goitre since puberty, but there had been a considerable and rapid enlargement for the past few months. This, together with the hardness, gave rise to a suspicion of

malignancy. It was not until the pathological report became available that we had any idea of the unusual nature of the swelling. Subsequent investigations showed slight patchy fibrosis in the lung fields and one characteristic punched-out area in the terminal phalanx of the left middle finger.

At thyroidectomy the gland was not adherent but was highly vascular.

A photograph of the specimen was shown together with photomicrographs. Dr. O. C. Lloyd reports the "typical appearances of sarcoidosis".

The case is shown not only as an uncommon goitre but to emphasize that sarcoidosis may occur in unusual sites, with the usual absence of constitutional symptoms, and may escape immediate recognition. From time to time these lesions have been found in almost every organ and tissue of the body. In this case the one presenting clinical feature was the very large, hard thyroid.

Endometrial Stricture of Small Intestine Simulating Crohn's Disease.—HENRY THOMPSON F.R.C.S.

Miss A. P., aged 47.

History.—For many years, diarrhœa associated with change of diet and environment during holidays.

For last five months, recurrent attacks of abdominal pain and diarrhœa lasting three to four days at four-week intervals. Slight passage of mucus. Marked constipation between attacks.

For last two months, colicky abdominal pain, starting in the epigastrium and radiating to right iliac fossa. At maximum intensity of pain there was a distension and swelling in right lower abdomen. The cessation of pain was associated with audible intestinal gurgling.

One week before admission, increased intensity of pain associated with vomiting.

The patient had not associated her symptoms with her periods, which were normal.

2.10.58: Admitted to St. Mark's Hospital as emergency.

On examination.—Well-nourished woman. Abdominal distension with hyper-resonant percussion note and tenderness in right iliac fossa.

Diagnosis: Crohn's disease with subacute intestinal obstruction.

Laparotomy.—Peritoneal surface of lower 15 in. (38 cm.) of ileum bright red, bound down to right pelvic wall and containing three strictures.

Both ovaries almost completely replaced by chocolate cysts. Two small endometrial implants on wall of sigmoid colon producing incomplete strictures.

Procedure: Resection of terminal 12 in. (30 cm.) of ileum. Ileo-cæcal valve embedded. End-to-side ileo-cæcostomy. Bilateral salpingo-oophorectomy. No surgery to sigmoid colon.

Leiomyoma of the Small Intestine.—F. G. ELLIS, F.R.C.S. (for S. H. WASS, M.S.).

H. B., male, aged 62, had severe melæna necessitating blood transfusion in 1956 and 1958. In 1956 examination of the abdomen was normal apart from a large right scrotal hernia containing the terminal ileum and proximal colon. Both testes were normal but in the sac a third solid swelling was found, of the size and consistency of a testis. Though its nature was uncertain it was not considered as a possible cause of his bleeding. After negative radiological investigations he was discharged. In 1958 after further bleeding a mass was felt in the right hypochondrium and a barium enema showed a probable carcinoma of the colon. The scrotal mass was unchanged.

At operation the mass in the right hypochondrium was found to be a mobile kidney. The colon was normal. The scrotal swelling was a solid spherical tumour in the wall of the small intestine. It was nearly all extraluminal but a small part of it had ulcerated through the mucosa and this was the site of bleeding. There was no clinical evidence of malignancy. Frozen section suggested leiomyosarcoma but after the paraffin section a diagnosis of non-malignant leiomyoma was made in spite of areas showing marked differences in cellular morphology.

The recent literature stresses the benign nature of these lesions and suggests that the term leiomyosarcoma should be abandoned and the tumours designated leiomyomas with varying degrees of differentiation.

Fibroma of Neck and Mediastinum. Removed by a New Surgical Approach.—P. R. ALLISON, F.R.C.S.

A. K., female, aged 7.

The tumour was noticed in January 1957 and had been slowly enlarging since. On three previous occasions operations had been performed for its removal (February, May and October, 1957) but on each occasion the operative procedure had to be stopped because of excessive hæmorrhage. A right Horner's syndrome was present. There was some aching in the right hand and a hoarse irritating cough with stridor.

On examination.—A nodular fixed mass occupied the lower half of the posterior triangle on the right side of the neck. X-rays showed it to extend down to the neck of the third rib. There was no evidence of muscle weakness or paralysis except that the right diaphragm was paralysed.

Operation (17.6.58).—A posterior approach to the right upper thoracic cavity was made by the following steps:

(1) An incision along the upper and medial borders of the right clavicle and scapula. The trapezius was detached from the spine of the scapula and clavicle and turned medially.

(2) The levator angulæ and the rhomboids were detached from the scapula and reflected medially, the scapula being allowed to come forward.

(3) The first three ribs were excised and their bundles divided.

This exposed the intrathoracic portion of the tumour which was fixed in the thoracic aperture and firmly adherent to the upper thoracic spinal bodies. The right subclavian artery and vein passed through the middle of the tumour. The tumour was divided in half at the thoracic inlet, which procedure enabled the subclavian vessels to be secured. The brachial plexus was dissected off the upper surface and the rest of the tumour removed. The blood supply to the right arm must now be from the lateral thoracic artery through anastomoses with the lower intercostals and vessels in the latissimus dorsi.

The tumour is lobulated and about 16×5 cm. in its long axis. It is partially encapsulated. The cut surface shows a whorled fibrous pattern with areas of congestion. Microscopically it is a fibroma with interlacing bundles of fibroblasts. There is no histological evidence of malignancy. There does not appear to be any association with nerve tissue and the tumour may possibly be related to the condition of juvenile fibromatosis described by Stout (1954, *Cancer*, **7**, 953).

Post-cricoid Carcinoma.—P. R. ALLISON, F.R.C.S.

I. W., female aged 37.

The illness commenced with dysphagia first noticed in September 1957. Œsophagoscopy a month later showed no abnormality. Improvement followed until February 1958 when dysphagia recurred. On May 20, an ulcer was seen in the post-cricoid region which biopsy showed to be a squamous cell carcinoma. No enlarged cervical lymph nodes were palpable.

Operation (18.6.58).—A total laryngo-pharyngectomy was performed together with removal of half the thyroid gland and a block dissection of both sides of the neck. A Roux loop was fashioned and brought up and anastomosed to the base of the tongue and oropharynx. The lower end of the Roux loop was inserted into the stomach.

The specimen shows an ulcer at the back of the thyroid and cricoid cartilages with raised edges and a necrotic shallow base.

Histology.—A moderately differentiated squamous cell carcinoma invading the submucosa but not the muscular layer of the pharynx. A small deposit of squamous cell carcinoma was present in one gland removed from the right side of the neck. The non-involved lymph nodes showed reactive changes and sinus catarrh but no evidence of invasion.

The following specimens were also shown:

Amyloid Disease of the Thyroid Gland.—Mr. G. E. MOLONEY.

(1) **Recurrent Ulceration in the Rectum after Sub-total Colectomy and Ileo-rectal Anastomosis for Ulcerative Colitis.** (2) **Recurrent Polyposis in the Rectum Five Years after Sub-total Colectomy and Ileo-rectal Anastomosis for Non-familial Polyposis of the Large Bowel.**—Mr. L. R. DE JODE (for Mr. CLIVE BUTLER).

Colloid Carcinoma of the Colon.—Mr. GUY BLACKBURN.

Hirschsprung's Disease.—Mr. IAN P. TODD.

"Blind Loop" Syndrome due to Tuberculous Ileal Strictures, with Enterolith.—Mr. P. KNIPE (for Mr. ANDREW DESMOND).

Lymphosarcoma of Breast.—Mr. R. S. HANDLEY.

Brodie's Tumour of Breast.—Mr. W. W. SLACK (for Mr. R. S. HANDLEY).

(1) **Aspergillosis.** (2) **Fat Embolism of the Lung.**—Mr. DONALD BARLOW.

(1) **Paratyphoid Empyema (excised).** (2) **Gastric Carcinoma Occurring in an Œsophagus Lined by Gastric Mucous Membrane.**—Professor P. R. ALLISON.

Œsophagus Lined by Gastric Mucous Membrane Treated by Resection.—Mr. G. WESTBURY (for Mr. R. COX).

(1) **Pseudosarcoma of Œsophagus.** (2) **Idiopathic Muscular Hypertrophy of Œsophagus Treated by Resection.**—Mr. M. VEIDENHEIMER (for Mr. R. H. FRANKLIN).

Localized Carcinoma of the Ampulla of Vater.—Colonel R. E. WATERSTON.

Two Cases of Congenital Biliary Atresia.—Dr. A. C. HUNT.

Bilateral Double Kidney.—Mr. GEOFFREY PARKER.

Section of Endocrinology

President—Professor F. T. G. PRUNTY, M.D., F.R.C.P.

Meeting
November 26, 1958

Thyrotoxicosis Developing in Recurrent Nodular Goitre with Focal Thyroiditis.—G. F. JOPLIN, M.R.C.P., and RUSSELL FRASER, M.D., F.R.C.P.

Miss C., aged 57.

1945: Partial thyroidectomy for pressure symptoms from non-toxic nodular goitre, present two years.

Histology.—Nodular thyroid. Acinar epithelium of normal height (consistent with euthyroid state). Numerous areas of epithelium show Askanazy cell change. There are quite numerous areas of lymphoid infiltration with occasional germinal centres, and also small areas of fine fibrosis, i.e. focal thyroiditis.

1952: Reviewed. Still clinically euthyroid, but goitre re-growing. ^{131}I test: forty-eight-hour urine (U_{48}) 47% (normal 35–70), T = 14·6 (normal 2·8–13). Iodide repletion test (10 mg./day for seven days, and re-test in six weeks): U_{48} 57%, T = 4·0, i.e. normal.

1953: Clinically euthyroid. ^{131}I test unchanged.

June 1957: Clinically borderline toxic; goitre larger. ^{131}I: U_{48} 15%, T = 11·7. After seven days' l-triiodothyronine: U_{48} 50%, T = 2·3. E.S.R. 5 mm. in the first hour (Westergren); electrophoretic protein pattern normal, zinc sulphate and thymol turbidity normal. Cholesterol 276 mg.%

November 1957: Clinically obvious thyrotoxicosis. No eye signs. ^{131}I: U_{48} 24%, T = 18·1. Neck uptake at forty-eight hours 78%. No suppression by l-triiodothyronine. Biopsy (Fig. 1) similar to 1945. E.S.R. 11 mm. in the first hour. Began carbimazole 15 mg. per day and sodium l-thyroxine 0·3 mg. daily. Failed to respond, until perchlorate added as well.

July 1958: Still under drug control, but now eyes watering. Lid lag, lid œdema present.

November 1958: Eyes worsening. Left-sided goitre, firm and nodular, of about 70 grams. E.S.R., proteins and turbidities normal.

Thyroid antibody tests (Dr. Deborah Doniach).—Thyroglobin precipitin test negative. Tanned red cell agglutination weak positive (1 : 25). Thyroid complement-fixation strong positive (1 : 64).

Biopsy.—Still lymphocytic foci, occasional fine fibrosis and widespread Askanazy cell change (Fig. 2).

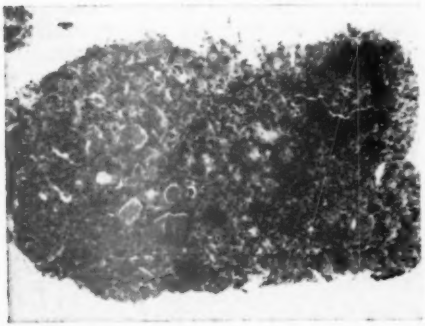


FIG. 1.—Thyroid biopsy November 1957, before any therapy. Lymphocytic infiltration is quite widespread. × 60.

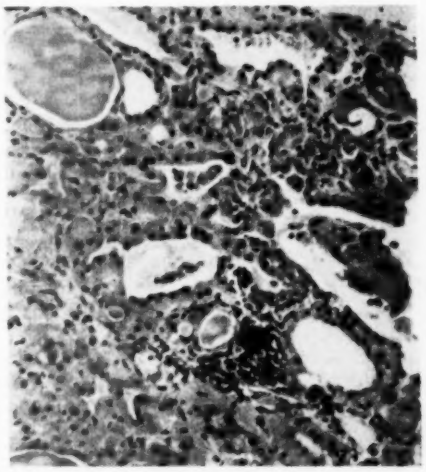


FIG. 2.—Thyroid biopsy July 1958. Askanazy change is widely seen, and a lymphocytic focus is present. × 158.

Comment.—This woman presents the interesting sequence of a long-standing non-toxic nodular goitre, known originally to show focal thyroiditis, now becoming frankly toxic—and still showing focal thyroiditis on biopsy. One might have expected that such a goitre, especially when partially excised, would lead to hypo-

thyroidism due to progression of the inflammatory process.

It is also of interest that Dr. Deborah Doniach has demonstrated a strongly positive complement-fixation test, and also a weakly positive tanned red cell agglutination—perhaps this correlates with the presence of the focal thyroiditis.

Lastly, the close correlation of the ^{131}I tests with the clinical thyroid status is shown: there was only a high uptake not suppressible when she became clinically toxic.

Thyrotoxicosis Merging into Hashimoto's Disease.—DEBORAH DONIACH, M.D. (for R. VAUGHAN HUDSON, F.R.C.S.).

C. H., male, aged 48. In February 1956 noticed thumping of the heart, sweating and heat intolerance, loss of weight of 2 st. with excessive appetite. On examination in October 1956 the patient had staring eyes, lid lag and lid retraction, warm skin and fine tremor of hands. The thyroid was diffusely enlarged, estimated weight 45 grams, of soft consistency with no thrill. Resting pulse rate 84–100, blood pressure 160/80, exophthalmometer readings R.23, L.22 mm. Provisional clinical diagnosis: diffuse small cervical goitre with stare, no exophthalmos, thyrotoxicosis of moderate severity.

Investigations.—B.M.R. = +20%. ^{131}I uptake 63% at three hours, 65% at twenty-four hours. Thyroglobulin precipitin test negative.

Treatment with carbimazole led to disappearance of all symptoms, and reduction in goitre size; an initial dose of 30 mg. was reduced to 5 mg. daily after three months. Seven months after onset of treatment the thyroid was barely palpable and very soft. The gland was still almost normal in size when a thyroglobulin precipitin was first noted in December 1957. The precipitin was weak since the Oudin double diffusion gel test, done on serial dilutions of serum, was only positive up to 1/2 serum dilution. The patient also had complement-fixing thyroid antibodies: C.F.T. gave positive results up to 1/64 serum dilutions using thyrotoxic thyroid gland extract as the antigen and 2 minimum haemolytic doses of complement (2MHD) for the test. Following a febrile cold in March 1958, tenderness and aching of the thyroid were noted for ten days and the goitre became firmer. The thyroglobulin precipitin became more strongly positive, and was visible up to 1/8 serum dilutions.

June 1958: Goitre firm, estimated weight 50 grams, not tender. No bruit could be heard, but the gland still showed increased pulsation and the patient was thought to be slightly hyperthyroid.

August 1958: Goitre more horseshoe shaped, estimated weight 60–80 grams. There was a recent increase in exophthalmos, R.27, L.25 mm. but without subjective eye symptoms. Gamma globulins were within the normal range, thymol turbidity 3 units, zinc sulphate turbidity 10 units, colloidal gold test negative. Patient still felt better when taking carbimazole 5 mg. daily. In October 1958 he had an attack of influenza with a temperature of 100·5° F., sore throat and running nose for three days. Since this illness his neck became larger; tenderness of the thyroid had been noticed again since September. Neck circumference increased by 1½ in., the goitre was now firm and lobulated, estimated weight well over 100 grams, and felt like a typical Hashimoto goitre. The patient appeared euthyroid and carbimazole was discontinued.

Needle biopsy 29.10.58 (Mr. R. Turner-Warwick).—Dr. Drew Thomson reported a typical lymphadenoid appearance with diffuse Askanazy cell change and lymphoid infiltration with plasma cells. The thyroid epithelium in unaffected areas showed loss of colloid and tall follicular cells characteristic of thyrotoxicosis treated with antithyroid drugs.

November 1958: The patient complained of a choking sensation and excessive lacrimation. His goitre had not decreased in size since stopping carbimazole; the eyes showed some supraorbital œdema and slight conjunctival injection; exophthalmometer readings were R.29, L.29 mm., diplopia could be elicited on looking to the extreme right and upwards. B.M.R. now +36%, pulse rate 98, blood pressure 130/80. An area of indurated swelling and erythema 3½ × 2 in., suggestive of pretibial myxœdema, was noted on the lateral aspect of both shins, above the ankles. The precipitin test was now positive up to 1/32 serum dilutions and the complement-fixation titre had risen to 1/512.

In December 1958 he was mildly thyrotoxic and losing weight. The thyroid was somewhat smaller and less tense but pressure symptoms were still troublesome. Exophthalmometer readings decreased to R.27, L.27 mm., supra-orbital œdema and conjunctival injection were still present and the patient complained of a "gritty feeling" in the left eye; orbital pressure was moderately raised on digital palpation. In view of the increasing pressure symptoms and the persistent hyperthyroidism, it was decided to operate. The certain consequence of myxœdema will need careful control and the possibility of aggravation of the ophthalmoplegia has to be faced as a possibility particularly in view of the high titre of thyroid antibodies.

Dr. Raymond Greene said that the fear of thyroidectomy in cases of exophthalmos and the treatment of exophthalmos with thyroxine both arose from the

dogma that exophthalmos was due to the excessive production of T.S.H., which was demonstrably untrue. Though an increase in exophthalmos *post* thyroidectomy was occasionally seen, it did not follow that it was *propter* thyroidectomy. The same argument might be applied to the treatment with thyroxine. Though improvement had, very rarely, been observed, it had as often been seen during many kinds of treatment or during no treatment at all. He had recently shown that D-thyroxine, which has a negligible metabolic effect, completely suppressed the production of T.S.H., but he had failed by this means to influence exophthalmos.

REFERENCE

GREENE, R., and FARRAN, H. E. A. (1958) *Brit. med. J.*, ii, 1057.

Professor Russell Fraser suggested that while thyroxine was not a treatment of exophthalmos, its continuous administration was an important way of preventing any worsening of exophthalmos following thyroidectomy or any other antithyroid treatment.

Mr. Barrie Jones: *Lacrimal disorders associated with thyroid disease.*—Although the precise cause of epiphora in thyroid disturbances is conjectural, the symptom may be a troublesome one. Patients presenting in eye clinics complaining of epiphora, in the absence of derangements of the lacrimal passages, fall, apart from those with rosacea, into two groups: those who are thyrotoxic and those who are myxœdematous. In each group treatment of the endocrine disorder cures the watering, usually with a gratifying promptness. Although there is some experimental evidence that rabbits secrete more tears when treated with thyroxine, it is not clear that this applies to man. It is likely that the lid retraction and diminished blinking of thyrotoxicosis leads to corneal exposure and increased irritation, which results in a reflex hypersecretion of tears. In some cases lid retraction might lead to eversion of the lacrimal punctum, but this appears to be uncommon. It has been suggested that myxœdematous changes in the tissues around the lacrimal passages might impair drainage, but the epiphora is sometimes relieved before visible change in facial appearance has resulted from treatment. Blinking is known to exert a pumping action on the tear sac and it is likely that the torpid lack of blinking in myxœdema is of importance.

Stein-Leventhal Syndrome.—ARNOLD BLOOM, M.D., M.R.C.P.

Mrs. P. R., aged 33. Periods began at age 12, continued regularly with normal loss for about eighteen months and then ceased. About this time she began to put on weight, she developed hair on her face and an increased growth of hair on the trunk. She has shaved every other day since the age of 15. She married ten years ago, normal libido. She has five sisters, none hirsute. There is no history of family diabetes.

On examination.—Heavily built (14 st.). Attitude feminine, voice not deep. Plethoric facies, greying hair on head, slight recession at temples, looks older than her years (Fig. 1). Heavy growth of hair on face and trunk, tendency to masculine escutcheon. Colourless striæ over lower abdomen. Pelvic examination: clitoris slightly enlarged, ovaries not palpable. Blood pressure varied from 140/85 to 180/105.

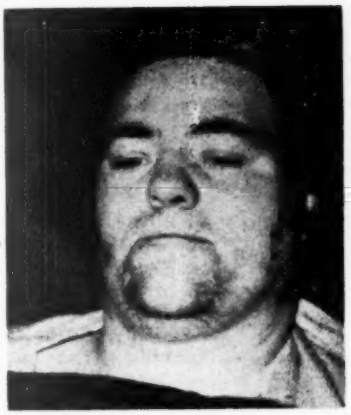


FIG. 1.

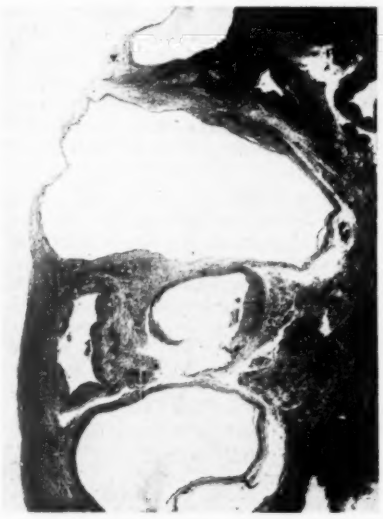


FIG. 2.—× 9.

Investigations.—17-ketosteroids 7·8 mg./twenty-four hours (average 7 estimations): total 17-hydroxycorticosteroids 9·8 mg./twenty-four hours (average 6 estimations), 39 mg./twenty-four hours on one occasion. Pregnanediol (Klopper) 2·2 and 5·9 mg./twenty-four hours. Glucose tolerance curve on two separate occasions:

fasting 97, 98 mg.%; thirty minutes after 100 grams glucose, 186, 140; one hour after, 217, 215; two and a half hours after, 177, 202 mg.%. Urine contained sugar. Hb 98%, W.B.C. 10,200, eosinophils 181. Vaginal smear: large squames with small pyknotic nuclei suggesting full œstrone action. X-ray skull: normal pituitary fossa.

Operation 24.4.58 (Mr. N. Stidolph).—Each ovary 2 × 1 in. with thick smooth fibrous covering and numerous small serous cysts on surface. Wedge of tissue removed from left ovary, right ovary split and everted. Both adrenals palpated, perhaps slightly thickened but no tumour. Section of ovarian tissue (Fig. 2) showed numerous follicular cysts lined by granulosa cells in most cases but in a few by theca interna cells in places infiltrating surrounding stroma, and in places luteinized. Section of skin showed the nuclear chromosomal pattern to be female in type (Dr. C. C. Bryson).

Post-operative course.—Had one normal menstruation and then amenorrhœa with temporary colostrum from breasts. Negative male toad pregnancy test.

Comment.—This patient typifies the Stein-Leventhal syndrome, showing amenorrhœa and hirsutism with polycystic ovaries. Despite normal 17-ketosteroids and total 17-hydroxycorticosteroid output in the urine, the clinical picture here suggests both increased androgenic and gluconeogenetic effects such as occur in adrenal cortical overactivity. The diabetic glucose tolerance curve is particularly interesting in this respect.

Dr. G. I. M. Swyer said it was necessary to expand the criteria for the syndrome as originally described by Stein and Leventhal. Obesity was certainly not an essential feature; hirsutism varied greatly in extent; and the disturbance of menstrual function was not confined to amenorrhoea. The only uniform feature was the bilateral ovarian enlargement—and even then the histology of the ovaries was inconstant. In his latest paper, Stein (1958) made no mention of obesity, referred to menometrorrhagia as well as amenorrhœa, and found hirsutism in only about 50% of his cases. *See also* Leventhal (1958).

REFERENCES

LEVENTHAL, M. L. (1958) *Amer. J. Obstet. Gynec.*, **76**, 825.

STEIN, I. F. (1958) *Int. J. Fertility*, **3**, 20.

Dr. Raymond Greene wished to make a semantic protest. He said that the Stein-Leventhal syndrome consisted of obesity, hypertrichosis, oligomenorrhœa and polycystic ovaries. Dr. Swyer's cases had, apparently, none of these characteristics. They showed interesting variations from the normal but they were not suffering from the Stein-Leventhal syndrome.

Dr. David Ferriman said that examination of an unselected series of women showed that about 10% presented some degree of hirsuties. Oligomenorrhœa was common in this group, and a tendency to infertility not infrequent. No examination of the ovaries was known to have been made in a consecutive series of such women—not surprisingly, since this would have involved laparotomy or at the least gynæcography in all. The incidence of polycystic ovaries in hirsuties was therefore unknown. It was possible that many cases reported under the title of Stein-Leventhal syndrome might be extreme examples of constitutional virilism. Polycystic ovaries could be produced in animals by injections of F.S.H., and their presence might be related to some hormonal disturbance in this type of patient.

Fröhlich's Syndrome.—D. CROOKE MORGAN, M.B. (for RAYMOND GREENE, D.M., F.R.C.P.).

B. B., male, aged 12. Referred to Dr. E. C. O. Jewesbury in 1952 when 6 years old. After a fall, it had been noticed that he was not using his right arm. Examination revealed a spastic hemiparesis on the right, while the left palpebral fissure and pupil appeared small. Owing to an error of development, his left forearm was absent. During the next four weeks, he experienced several episodes of weakness in which he appeared to be unaware of his surroundings. At the end of this time, the margins of his optic discs were found to be blurred.

The patient was referred to Mr. Leslie Oliver who carried out Myodil ventriculography (Figs. 1 and 2). This appeared to show a large brain-stem tumour, and the diagnosis was confirmed by exploration. The tumour was inoperable.

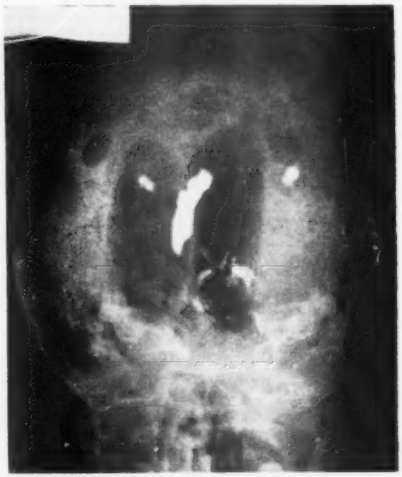


FIG. 1.—Ventriculogram, A.P. view. Dilated lateral ventricles and lateral displacement of 3rd ventricle and aqueduct.

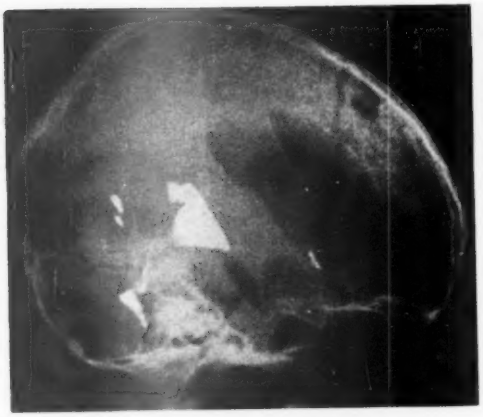


FIG. 2.—Ventriculogram, lateral view. Elevation of the aqueduct and floor of 3rd ventricle.

Histological examination of a biopsy specimen suggested that it was an astrocytoma.

The expected deterioration in his condition did not occur, and over the next five years there was no change in the neurological signs. In April 1958, he was referred to Dr. Raymond Greene complaining that he was being called "Sabrina" at school. He was found to be a fat boy without axillary hair, but with a little pubic hair. Slight gynæcomastia was present. His genitalia were just within normal limits for his age. He appeared to be euphoric, while the left Horner's syndrome was now definite and the right hemiparesis persisted. The exact time at which his appetite increased after the operation could not be exactly determined. His condition remained stationary over the next six months apart from a loss in weight induced by a low-carbohydrate diet (Fig. 3).

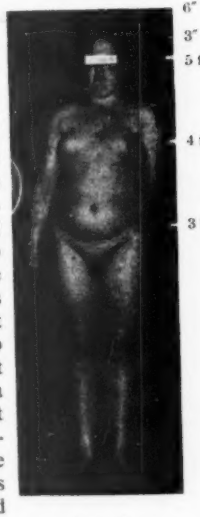


FIG. 3.

Investigations (October 1958).—X-ray skull: No evidence of raised intracranial pressure; pituitary fossa small; clinoid processes intact. Insulin sensitivity test normal. Urinary 17-ketosteroids 4·4 mg./twenty-four hours, 17-hydroxycorticoids 4·8 mg./twenty-four hours. Serum cholesterol 247 mg.%. Radioactive iodine excretion gave a result within the limits of hypothyroidism.

The course of Fröhlich's case is contained in several reports reviewed by Bruch (1939). It is perhaps dangerous to make this diagnosis before ensuring that puberty is indeed delayed. However, the clinical condition of the case reported here is comparable with that of Fröhlich's case when the latter was first seen. Moreover the ventriculogram and operation findings give firm evidence of a lesion affecting the hypothalamus.

Disturbances of hypothalamic function are considered to be the primary cause of the syndrome, the pituitary gland often being intact. Obesity and delayed sexual development, however, are but two signs of hypothalamic damage. In a review of 60 cases in which the hypothalamus was involved by disease, Bauer (1954) found that hypogonadism occurred in 19, and obesity in 15 cases. Somnolence, diabetes insipidus, disturbances in temperature regulation and mental changes were just as common. It would therefore seem that Fröhlich's syndrome makes an artificial division of disturbances caused by a hypothalamic lesion and the term might well be discarded.

REFERENCES

BAUER, H. G. (1954) *J. clin. Endocrin.*, **14**, 13.
BRUCH, H. (1939) *Amer. J. Dis. Child.*, **58**, 1282.

Dr. Raymond Greene said he had encouraged Dr. Morgan to show this case because in thirty years of practice it was the first example he had seen of the true syndrome, consisting of obesity, sexual retardation and an intracranial tumour. It was curious that so rare a condition should be diagnosed so often by general practitioners. He had a fat boy referred to him about once a month with this label wrongly applied.

Pseudohypoparathyroidism.—S. HALL, M.B. (for D. FERRIMAN, D.M., M.R.C.P.).

B. K., male, born October 1951.

Patient was referred in March 1957 to Dr. I. G. Wickes (by whose courtesy the case is shown) because of retarded mental development and recent anorexia and constipation. No visual disturbance, tetany, bronchospasm or convulsions.

Previous history.—Birth weight 7 lb. 5 oz. Bronchopneumonia at 10 weeks; noted then to be "odd looking" with marked micrognathia. Sat at 12 months, walked at 2½ years. Few words at 2 years.

Family history.—Three siblings. No history of mental defect, epilepsy or visual disturbance. No abnormal appearance of hands or face.

Physical findings.—Placid and amiable. Could walk but not run. Could not form sentences or count. Rather slow in his reactions. Round-faced. Broad hands and short fingers. Height

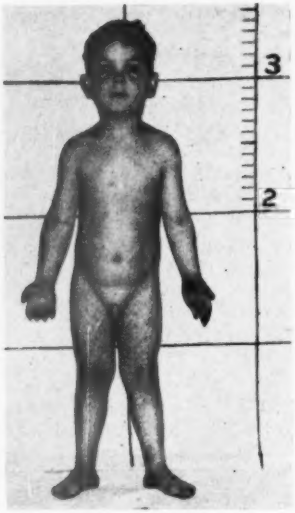


FIG. 1.

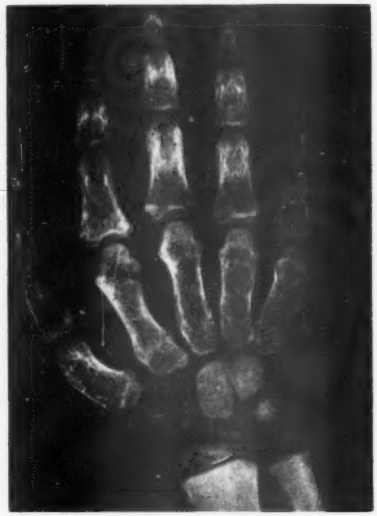


FIG. 2.

39¾ in. (50th percentile at this age 43¾ in.). Later a small chalky deposit noted on the 5th right finger. Skin and hair appeared normal. No cataracts (Fig. 1).

Investigations.—Bone age same as chronological age. Femoral heads normal. Serum cholesterol 244 mg./100 ml. ^{131}I uptake 24% at two hours, 25% at twenty-four hours, neck/thigh ratio at two hours 1·9 : 1. Urine: No abnormality; Sulkowitch test negative. Blood urea 30 mg./100 ml. W.R. and Kahn negative. Serum calcium 8·3, phosphorus 8·2 mg./100 ml., alkaline phosphatase 10 K.A. units.

X-rays: Skull: no basal calcification. Hands and feet: short metacarpals and metatarsals with cyst-like areas consistent with a dyschondroplasia (Fig. 2). The rest of the skeleton showed no abnormalities.

The results of two Ellsworth-Howard tests were equivocal.

I.Q. (Professor Aubrey Lewis) 59 on Terman-Merrill scale.

The patient was treated with vitamin D 80,000 units daily, later reduced to 40,000 units daily. He has grown 3½ in. in fifteen months, and his I.Q. has improved to 78.

Comment.—The combination of abnormal serum calcium and phosphorus figures, peculiar radiological changes in the hands and feet and subcutaneous calcification is consistent with the syndrome described by Albright *et al.* (1942) and called by them pseudohypoparathyroidism. Unfortunately the results of the Ellsworth-Howard tests in our case are equivocal. The significance of this test is, however, in question. Originally it was regarded as indicating a failure of end-organ response to parathormone. A failure of response has been noted, however, in other conditions such as severe post-operative hypoparathyroidism and idiopathic steatorrhœa. On the other hand, cases of pseudohypoparathyroidism have been reported with a normal response to parathormone, and normal serum calcium and phosphorus figures; these have sometimes been labelled pseudo-pseudohypoparathyroidism and regarded as representing a distinct if related condition. However, two families (Bille, 1952; Buchs, 1954) contain patients suffering from both pseudohypoparathyroidism and pseudo-pseudohypoparathyroidism. Moreover, scrutiny of the case reports of pseudohypoparathyroidism show that the failure of response to parathormone is sometimes incomplete. These facts suggest that the two conditions are one and the same disease, the expression of which is sometimes incomplete.

The condition is inherited as a dominant. The metabolic disturbance responds well to vitamin D.

REFERENCES

ALBRIGHT, F., BURNETT, C. H., SMITH, P. H., and PARSON, W. (1942) *Endocrinology*, **30**, 922.
BILLE, B. S. V. (1952) *Acta pædiat., Stockh.*, **41**, 380.
BUCHS, S. (1954) *Ann. pædiat.*, **183**, 65.

[*Meeting to be continued*]

for control of inflammation

This new Lederle product provides a new approach in the management of trauma and inflammation. It presents streptokinase in a form that is directly absorbed by the buccal route. VARIDASE Buccal Tablets control inflammatory reaction, reduce swelling and relieve associated pain — without mucosal irritation or allergic manifestation. The Buccal Tablets also allow better access of antibiotics to an inflamed area.

Varidase Buccal Tablets can also be used with antibiotics, in infective conditions such as cellulitis, abscesses, thrombophlebitis, sinusitis, chronic bronchitis, leg ulcers, chronic bronchiectasis. Each tablet contains streptokinase 10,000 units and streptodornase 2,500 units.

Dosage: One tablet four times a day for a minimum of 3 days. The tablets to be placed in the buccal sulcus and allowed to dissolve.

Packing and Basic N.H.S. cost 12 *tablets* £1 1s. 8d.

Lederle

LEDERLE LABORATORIES
a division of
CYANAMID OF GREAT BRITAIN LTD. London W.C.2

CYANAMID

Section of Ophthalmology

President—J. R. WHEELER, F.R.C.S.

Meeting
November 13, 1958

DISCUSSION ON NEW CONCEPTS OF EYE MOVEMENT [*Abridged*]

Dr. R. A. Weale (London):

The Problem of False Torsion

It has often been stated that when normal eyes move from the "straight ahead" position to fixate a point, say, at two o'clock—the head remaining fixed—the retinal vertical meridian and an external plumb-line cannot be made to coincide by any orthogonal system of projection. An irrelevant exception to this generalization can be ignored. This finding of apparent non-coincidence, based largely on after-image experiments, has led to the conclusion that the eyes suffer torsion. In order to distinguish this from "wheel movements" (Helmholtz's *Raddrehungen*) which the eye can undergo only involuntarily in the "straight-ahead" position, the term torsion is qualified by calling it "false". Márquez (1949) has dealt with the validity of the after-image experiments, and it is surprising that an objective study of the problem appears to have been attempted only once.

Whether or not torsion takes place, i.e. whether the retinal meridian remains vertical, can be settled photographically. Moses (1950) photographed the eye when it was looking straight ahead and again at increasing vertical elevations and horizontal deflections up to a maximum of 30 degrees, and claims that his results are consistent with Donders' law (cf. Maddox, 1898). This work can be criticized on three grounds: first, only one observer appears to have been studied; secondly, the photographs were taken along the fixation axis only in the zero position; and thirdly, it would seem from the photographs that the plumb-line which indicated the true vertical was actually swinging, the photograph being taken at a moment which would increase the angle of torsion.

In the present experiments, photographs were taken with two cameras. One of them pointed along the fixation axis of the subject's right eye in the primary position, the other along a line, inclined 45 degrees upward and 45 degrees temporally. In actual fact, a right-angled two-inch prism, the hypotenuse of which was silvered, was placed close to the eye. The prism deviated the beam so that the camera could be located at a convenient level instead of somewhere near the ceiling. A plumb-line was so suspended as to be visible by both cameras. All seven observers (2 women, 5 men) were instructed to cover but not to close the left eye. The size of the pupil was kept reduced by means of high background illumination.

There is no particular merit in either the retinal or iridal vertical meridian; consequently, any two well-defined marks on, or close to, the iris can be selected to determine the amount of torsion. Great care has to be taken, however, to ensure

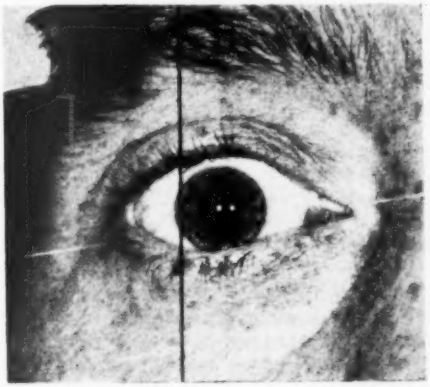


FIG. 1A.—The eye in its straight-ahead position.

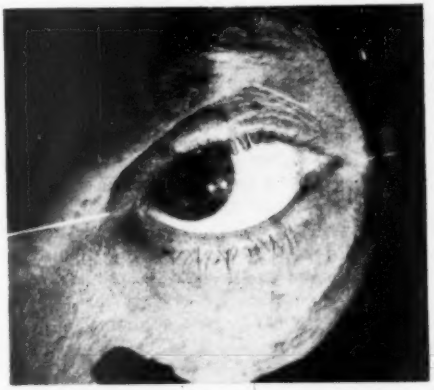


FIG. 1B.—The eye fixating in a direction of 45 degrees upward and temporally.

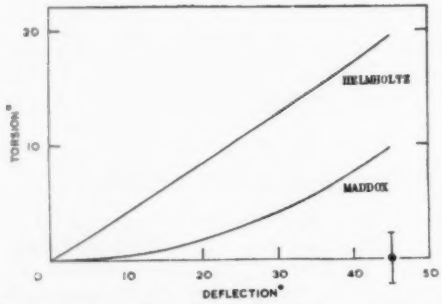


FIG. 2.—Angle of torsion (ordinate) as a function of the angle of deflection (abscissa) at an elevation of 45 degrees.

correctness of the identification of the marks. With the available material an accuracy to within one degree was easy, a greater accuracy unnecessary. A typical set of photographs is shown in Fig. 1. The difference between the angles included by the line through two marks and the plumb-line respectively gives a measure of torsion. The average of seven experiments done each on one subject happens to be zero (Fig. 2). The standard error of the mean shows this result to differ significantly from Maddox' formula and *eo ipso* from that of Helmholtz (1924). A random selection of any four of the seven individual data would not invalidate these deductions.

Although it may happen that any one person will exhibit ocular torsion when his eyes move from a cardinal to a non-cardinal position, on the average "false" torsion does not seem to occur. This finding calls into question the validity of the laws of both Donders and Listing (cf. Maddox, 1898). A consistent way of resolving eye movements about a horizontal and vertical axis respectively while, at the same time, accounting for the absence of "false" torsion is as follows: in moving from any one into any other position, the eye-ball can be considered to turn about its own horizontal, and about the orbital vertical axis. This system is reminiscent of the gimbal suspension of a marine compass which enables the compass to stay almost unaffected by the motion of the ship. If "false" torsion does not exist, it would appear to follow that any distinctions between primary, secondary, tertiary, cardinal and non-cardinal positions of the eye are irrelevant. It would also follow that the relation between the retinal image and the retina is independent of the position of the eye—a matter of some physiological interest.

I should like to thank the staff of the Department of Medical Illustration, Institute of Ophthalmology, for their ready help in this experiment.

REFERENCES

HELMHOLTZ, H. L. F. von (1925) Physiological Optics. Translated from 3rd German edit. by J. P. C. Southall. Menasha, Wisconsin; Vol. III, para 27.
MADDOX, E. E. (1898) Tests and Studies of the Ocular Muscles. Bristol; p. 47.
MÁRQUEZ, M. (1949) *Arch. Ophthal., Chicago*, **41**, 704.
MOSES, R. A. (1950) *Arch. Ophthal., Chicago*, **44**, 136.

Dr. P. A. Merton (Cambridge):

Compensatory Rolling Movements of the Eyes (Film)

In order that vision should be distinct it is necessary that a sharp image be formed on the retina and that this image should remain stationary on the retina while information is extracted. For foveal vision of full acuity it is probably necessary that the rate of movement of the image over the retina should not be more than a very few foveal cones per second. This corresponds to a rate of change of direction of the visual axis of a few minutes of arc per second. Such a very high stability is not difficult to achieve when the body is at rest but when the body is moving about, running for instance, the task is one which could not be carried out, so far as I know, by any man-made stabilized platform. The human vestibular system, however, certainly does extremely well (exactly how well has not been measured) at keeping the image stationary.

The vestibular reflexes that tend to keep the visual axis pointing in the same direction when the head is turned from side to side or moved up and down, are well known. But these reflexes will not suffice to keep the image stationary if the head rotates about the optic axis. Such movements, which are conveniently referred to as "rolling" movements, result in a relative twisting of the image on the retina even though the fixation point remains unchanged. For foveal vision such rolling movements are much less important than ordinary translational movements, because in terms of cones per second the rate of movement will be small near the axis. The fixation area of the fovea where acuity is greatest is thought to have a radius of roughly 20 cones' breadth (50μ) so that, if the fixation point is in the centre, a rate of (circumferential) movement of the image of 1 cone per second at the periphery of the fixation area corresponds to a rate of rolling of the eye about its visual axis of $\frac{360}{2\pi \times 20} \simeq 3$ degrees per second. In other words, rolling movements can probably be tolerated some 200 times faster than translational movements because the radius of the fixation area is only about 1/200 of the radius of the eye.

The head often makes rolling movements, or movements that have a component of roll, faster than 3 degrees per second. The film demon-

strated that the vestibular system stabilizes the eye against such rolling movements to about the expected accuracy. The subject's eye was photographed while he was swung from side to side in a special swing of which the axis of rotation corresponded with the optic axis of the eye. The frequency was one cycle in 1·5 seconds. With a swing movement of 20 degrees total (10 degrees either side of vertical) the eye only rolled through about 5 degrees (i.e. the relative movement of the eye in the head was about 15 degrees). Superimposed on the smooth sinusoidal eye movement were brief saccadic rolling movements. Probably the saccades correspond to changes of fixation point and are to be taken to indicate that the compensating rolling movements are not concerned in stabilizing the retinal horizon relative to the true horizontal, but that they stabilize the eye only during a fixational pause. At the next change of fixation point the stabilization "slips" and the eye rolls rapidly to a more convenient attitude.

The film also showed the complete absence of compensatory rolling in two patients who had lost labyrinthine function.

REFERENCES

DAVIES, T., and MERTON, P. A. (1958) *J. Physiol.*, **140**, 27P.
MERTON, P. A. (1956) *J. Physiol.*, **132**, 25P.

Dr. G. Melvill Jones[1] (Farnborough):

Vestibular Interference with Vision in Flight

Dr. Merton has indicated how vestibular signals assist the eyes in maintenance of a steady image upon the retina during short turning movements of the head. When turning movements are prolonged, errors develop in the signals which then become misleading and tend to cause eye movements appropriate to following the illusion of turning but quite inappropriate to the actual event. In man's normal environment on the ground, when turning movements are of short duration time does not usually permit development of significant errors and the system affords good functional assistance to vision. But during flight, turning movements are usually more prolonged, as in a banked turn, or a loop, or during a rolling manœuvre, or when spinning, and time frequently does permit the development of serious errors in the vestibular system, which then feeds misleading signals into the central nervous system.

The point in question is, can these signals exercise sufficient influence in the visual mechanism to cause inappropriate movements of the eyes during flight? For, should this prove to be the case, information about orientation derived from the eyes might well prove to be as misleading as that from vestibular sources. If this occurs on the ground, proprioception can still be relied upon to detect the true vertical. But in the air a pilot is denied this information on account of the forward and radial accelerations imposed in all circumstances other than steady straight flight, and consequently the significance of vestibular interference with vision is greatly emphasized in the flight environment.

A programme of research has recently been initiated at the Institute of Aviation Medicine to investigate to what extent this factor can interfere with the ability of a pilot to fly an aeroplane. The apparatus developed for this purpose consists in the main of a ciné camera mounted on a conventional flying headgear and carrying a periscope so arranged as to pipe the image of one eye

[1]The Author is working for the Royal Air Force on the external staff of the Medical Research Council. The material contained in this paper was presented at the 1st International Congress of Aeronautical Sciences in Madrid, September 1958, the proceedings of which are published by Pergamon Press.

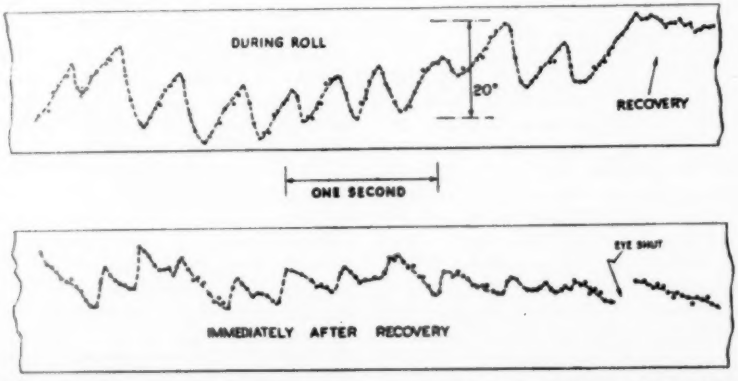


FIG. 1.—In flight record of rotational eye movements during and immediately after a 12-second 4-turn roll.

through two right angles into the lens of the camera. In this way ciné records can be taken in flight in which, since the camera is fixed to the head, all movement shown is of the eye relative to the skull. A technique has been devised for analysing these films and Fig. 1 shows the results obtained during and after a 12-second 4-turn roll in a Hunter aircraft. The record is of rotational nystagmoid eye movements (i.e. about the fore-aft axis of the eye) ordinate being angular displacement, abscissa time. During the roll the slow phase of the nystagmus is in a direction appropriate to maintenance of a steady image upon the retina. But after recovery, when the aircraft was stationary relative to the horizon, a reverse nystagmoid movement can be seen to have taken place, the angular velocity of the slow phase, as depicted by the slope of the line, dying away gradually over the course of several seconds.

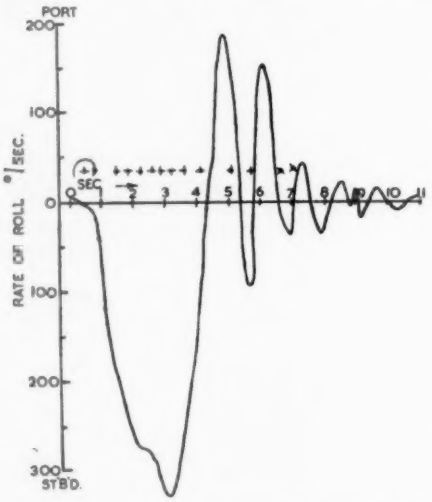


FIG. 2.—Rapid rolling manœuvre in which loss of control occurred.

During this period the image of the horizon must have been turning upon the retina when in reality there was no relative motion between horizon and aircraft and the question arises, how does the pilot interpret what he sees? Certainly in practice pilots do experience difficulty in rapid rolling manœuvres. Fig. 2 shows the time course of rate of roll of an aircraft during a rapid rolling manœuvre in which complete loss of control occurred. The pilot initiated the roll to the right with a high angular acceleration and on approaching 1 rev. per sec. he decided to recover. His rate of rotation steadily decreased, but instead of coming to a halt as intended he went into a rapid roll into the other direction. Thereafter he completely lost his bearings and wisely took hands and feet off the controls, when the aircraft recovered of its own accord on account of its intrinsic aerodynamic stability.

In conclusion it would appear that there are occasions when vestibular signals can interfere with vision in flight and it seems that here is an interesting field for further investigation.

Dr. P. A. Merton (in discussion on Dr. Weale's paper): Suppose a square figure is placed at a considerable distance in front of an observer so that it subtends only a small angle, say a degree, at his eye. Then as the subject fixates each corner of the square the images on his fovea of the lines that make up the corners will make an angle of almost precisely 90 degrees on his retina. But if the subject moves close to the figure (the centre of it remaining straight in front of him) so that a large diagonal movement of his eyeball is necessary in order for him to fixate the corners, then the images of the lines that make up the corners will meet on his fovea at an obtuse angle. (If he could move so close that his eye was in the plane of the figure and could still turn his eyeball so as to look at each corner in turn, they would all look like straight lines, hence it is clear that as the subject approaches the figure the angle of the images of the corners increases from 90 degrees to 180 degrees).

Suppose now that at the centre of the figure is drawn a cross, as in Fig. 1. The subject fixates the cross until he has an after-image of it, and he then fixates one of the corners of the square. The lines on his fovea of the after-image of the main arms of the cross are at 90 degrees to each other, but the images of the lines that make up the corner of the square meet at more than 90 degrees. Clearly the two cannot superimpose. How, then, are they orientated relative to each other on his fovea? Listing's law says that they are orientated so that the after-image of the diagnonal drawn on the cross coincides with the image of the diagonal at the corner. The excess of the obtuse angle over 90 degrees is therefore shared equally between the two main arms of the cross so that the after-images of the two arms of the cross make equal angles with the arms of the corner and lie inside them. These small equal angles, marked θ in Fig. 1, are the angles of torsion referred to in the exposition of Listing's law. Perhaps Listing's law is most easily understood in the form that there is no torsion of the after-images of diagonals. This way of putting it emphasizes that Listing's law prescribes the simplest and most symmetrical way for the eye to move.

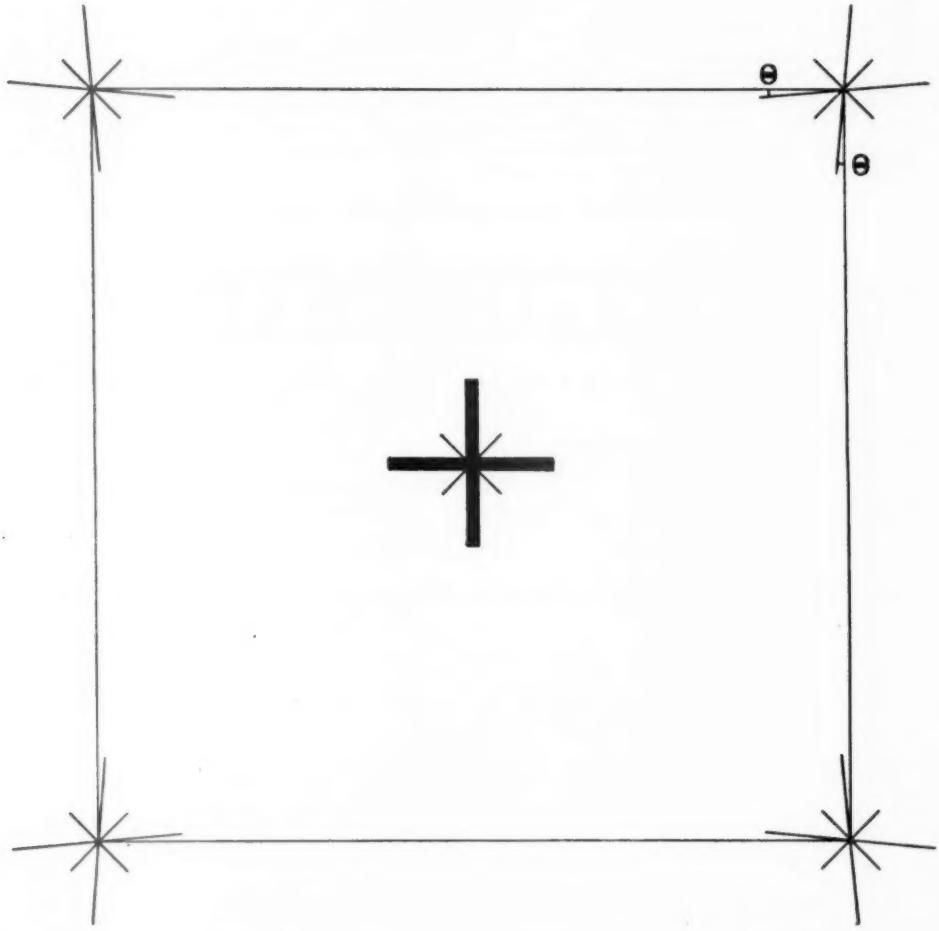


FIG. 1.—Figure for testing Listing's law of ocular movements. Cover one eye; hold this figure 5 in. from the other eye with the central cross in front of the pupil. If necessary use a + 8 dioptre lens. Steadily fixate the centre of the cross for a minute or two, in a bright light, until a good after-image is obtained. Then, without moving the figure or the head, move the eye to fixate one of the corners of the figure. The after-image of the cross will then superimpose on the cross drawn there, the angles of which are 79·6 degrees and 100·4 degrees instead of 90 degrees. The "angles of torsion", θ, are marked and are 5·2 degrees for this viewing distance of 5 in. The after-images of the diagonals show no torsion. (The after-image will probably be seen better if the illumination of the page is reduced.)

I hope I have made it clear that when the eye moves diagonally there must be apparent torsion for after-images in some directions, because an obtuse angle will not superimpose on a right angle. Which lines suffer apparent torsion and which do not is a matter of fact. Listing's law states one possible result, one which I believe to be correct, and which the reader can himself confirm with the aid of Fig. 1. Dr. Weale does not believe it. I would like to ask him just how, on his theory, he would fit the after-image of the cross into the obtuse angle made by the image of the corner of the square. It must have some definite orientation but he has not yet said in what way his orientation differs from the very simple and symmetrical orientation proposed by Listing and proved by Helmholtz.

Dr. Weale, in reply: I am grateful for Dr. Merton's comments, but, unlike him, I do not

think that the matter is one of faith. It is, as he says, a fact that after-images of lines inclined at 45 degrees to the horizontal do not "tort", but it can also be shown, as I think I have done, that the average vertical iridal meridian remains vertical in the experiment I have described. I agree with Maddox and more particularly with Márquez in their view that the approach of Helmholtz was mistaken if only because he failed to consider problems of perspective. If the screen on which the after-image is projected is spherical instead of plane as in Dr. Merton's example, the problem of the diagonals is solved automatically because the obtuse angles mentioned by Dr. Merton cease to exist.

Meeting
December 11, 1958

A DISCUSSION was held on the following unusual cases:

Intra-lenticular Foreign Body.—Mr. J. W. E. CORY.

Avulsion of Left Optic Nerve with Right Temporal Hemianopia.—Mr. E. F. KING.

Osteomyelitis of the Lesser Wing of Sphenoid in a Child.—Mr. J. MINTON.

Increasing Astigmatism due to Probable Melanoma of Ciliary Body.—Mr. P. MCG. MOFFATT.

Glaucoma Following Use of Homatropine in Refraction.—Mr. F. A. WILLIAMSON-NOBLE.

Chromophobe Adenoma.—Mr. C. A. G. COOK (for Mr. F. LAW).

Section of Dermatology

President—JOHN T. INGRAM, M.D., F.R.C.P.

Meeting
October 16, 1958

Behcet's Syndrome.—BRIAN RUSSELL, M.D., F.R.C.P.

M. M., female, aged 21. Housewife.

History.—Five and a half years ago: ulceration of mouth, vulva and perineum; the oral lesions cleared in one week, the other lesions in one month. Five years ago: Pyrexia and sore throat, followed by larger, more painful vulval ulceration, which has recurred two to four times a year with circular, sloughing ulcers around the edge of the tongue and hard-edged, irregular, ulcerated, purulent areas extending over the labia minora and perineum.

Antibiotics, hydrocortisone injected locally and Proctocaine gave temporary relief. One year ago given prednisone 10 mg. daily. Healing occurred but there was relapse on smaller dosage.

On examination.—Irregular scarred areas on sides of tongue and on buccal mucosa. Ulceration and scarring of perineum and vulva with partial destruction of labia minora.

Investigations.—Persistently raised E.S.R. and mild anæmia. Biopsy from vulva: acute inflammation, numerous focal collections of polymorphs, often around capillaries. Focal fibrinoid necrosis of one arteriole.

Comments.—Behcet (1940) defined the syndrome as an illness lasting many years in which three kinds of symptoms are prominent: (1) Transient aphthous changes in the mouth; (2) Ulceration of the genitalia; (3) Attacks of iritis (not always present).

This patient has not had iritis, erythema nodosum, furunculosis, thrombophlebitis, joint pains or manifestations in the central nervous system. The condition has been less severe since she has been treated with prednisone 10 mg. a day but she has recently married and it is possible that the improvement is related to this, the disease having started when her engagement was broken, at her mother's instigation. The marriage has not been consummated because of dyspareunia.

REFERENCE

BEHCET, H. (1940) *Dermatologica*, **81**, 73.

Dr. F. F. Hellier: I would like to point out that in 1934, several years before Behcet wrote his article, Whitwell described patients with ulcers of the mouth and vulva associated with which were certain skin lesions and also eye changes. It is a pity his paper has been neglected as he certainly had priority over Behcet.

These patients sometimes show serious central nervous system lesions. We had a case recently in Leeds which was diagnosed in the Neurological Department as disseminated sclerosis. The prognosis is not good in this type and any case of buccal and vulval ulceration should be regarded seriously because of the possible though uncommon threat of such complications. For therapy I have tried a wide range of drugs including antibiotics, steroids, gamma globulin and sedatives but, whilst one gets occasional or temporary successes, no treatment really seems to have constant beneficial effect.

REFERENCE

WHITWELL, G. P. B. (1934) *Brit. J. Derm.*, **46**, 414.

Dr. G. B. Dowling: Whitwell (1934) described the clinical syndrome on the basis of 3 cases. He described in his first patient, a man aged 34, recurrent iritis and mouth ulcers which had been present for sixteen years. These were associated with attacks of a papulo-pustular eruption of the nape of the neck which preceded the attacks of iritis and mouth ulcers by a few days, and lesions of the erythema nodosum type. In the second patient, a female aged 29, mouth and vulval ulcers were associated with erythema nodosum-like lesions. This patient also suffered an attack of acute sudden œdema of the right leg which persisted; no thrombosed vein could be felt. The third patient, a female aged 32, had mouth and vulval ulcers only. Whitwell remarked that there was a relatively unexplored syndrome of ulcers of the mouth accompanied by embolic lesions elsewhere. It was possible, too, that eye lesions might occur as reported in his first case.

Behcet's (1938) clinical description is also based on 3 cases. The features described are: ulcers of the mouth and genital region which differ from aphthous ulcers, being more like Lipschütz ulcers or esthiomene; conjunctivitis going on sometimes to iritis; recurring erythema nodosum-like lesions (seen in 1 of the 3 patients), and in 1 case acneiform attacks affecting the forehead, face and the nape of the neck. He further described the histology of the necrotic ulcers in some detail, observing in the sections very small round bodies, partly intra- and partly extra-cellular. He thought these bodies resembled the primitive corpuscles of variola and pointed to a virus origin of the disease. Behcet makes no reference to Whitwell's clinical description published four years earlier.

REFERENCES

BEHCET, H. (1938) *Bull. Soc. franç. Derm. Syph.*, **45**, 420.
WHITWELL, G. P. B. (1934) *Brit. J. Derm.*, **46**, 414.

Dr. L. Forman: Behcet's disease in its fully developed potential is a serious one because of the involvement of one or both eyes, with blindness, or disease of the central nervous system, which in some 50% of the cases leads to death. Again, the nodes on the limbs may be due to thrombophlebitis of small vessels, but there has been involvement of large vessels, e.g. inferior vena cava in Dr. Prosser Thomas's case, and superior vena cava in a case which I have shown.

REFERENCE

THOMAS, E. W. P. (1947) *Brit. med. J.*, i, 14.

Dr. P. M. Inman: Helen Curth (1956*a*, *b*), believes that striking improvement is brought about by blood transfusions or gamma globulin injections.

REFERENCES

CURTH, H. O. (1956*a*) *Ann. Derm. Syph., Paris*, **83**, 130.
—— (1956*b*) *Arch. Derm. Syph. Chicago*, **74**, 439.

Dr. I. B. Sneddon: We have tried gamma globulin in 12 cases and in none of them was there any improvement. I think Dr. R. E. Church still believes that psychogenic factors play a considerable part in the onset of aphthous ulcers. There is often a recurring death theme. Recently we treated a girl of 24 whose 3 brothers aged 34, 30 and 28 had all died suddenly and, following the deaths, she started with mouth ulcers.

The President: I feel that ætiologically there is a psychological association in this case. The onset followed a broken engagement, and I think a little homely psychology and Largactil probably better than steroids.

Cutaneous Arteriolitis with Splenomegaly.—B. BUCHANAN, M.B. (for S. C. GOLD, M.D., F.R.C.P.).

Mrs. J. K., aged 61. Housewife.

History.—A four-year history of "lumps" coming up on her legs. These are small (*circa* 5 mm.) raised red lesions which tend to become black in the centre later and gradually fade over three to four days. The lesions appear in crops, especially after she has been standing for a long time. Bed rest helps, but tends to alter the distribution so that they appear more on the buttocks, and latterly a few have appeared on the trunk and inner aspect of arms. Some have formed "ulcers" round the ankles.

No seasonal variation. No medicines have been taken. No joint swelling, abdominal symptoms, bleeding tendency or systemic upset.

On examination.—Papulo-purpuric rash on legs, buttock, and to a lesser extent on trunk and arms. Splenomegaly—3 fingerbreadths below costal margin.

Investigations.—E.S.R. 48 mm. in the first hour (Westergren). Hæmoglobin 10·1 grams % (68%)—normochromic normocytic. Platelets 100,000–250,000/c.mm. W.B.C. 3,000–5,000, normal differential count. Marrow normal. L.E. cells absent on three occasions.

Plasma proteins: Normal electrophoretic strip, but there are cryoglobulins present in the gamma fraction, which precipitate out at 29°–30° C.

Urine: No abnormality, especially no R.B.C.s.

Biopsy.—Section shows an area of necrosis in the dermis which is infiltrated with a number of inflammatory cells. The nuclei of many of these cells are pyknotic and there is some liquefaction of the basal layer. In this section there is no evidence of fibrinoid changes in capillaries or arterioles (Fig. 1).

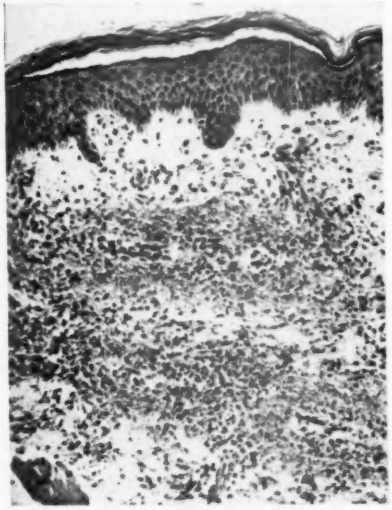


FIG. 1.

A previous section seen by Dr. I. Whimster was reported as follows: Intense fibrinoid necrosis in superficial vessels with hæmorrhage and patchy dermal infarction. The appearances are those of the erythema multiforme group.

Dr. S. C. Gold: We show this patient to-day as the condition presents some difficulty in classification. The splenomegaly, which is such a feature, is unusual in patients with cutaneous arteriolitis of the Gougerot pattern. A striking feature of the purpuric lesions is that their distribution is dictated largely by gravity and morphologically they are distinct from the usual anaphylactoid ones; some show necrosis enough to result in marked scarring, particularly around the ankles.

One of Ruiter's patients was supposedly a case of barbiturate sensitivity, but there was nothing to suggest such a process in our patient.

The President: I should not have thought this was arteritis of the polyarteritis type; it may be tied up with the spleen. Would it be worth doing a laparotomy?

Dr. D. S. Wilkinson: It is indeed very difficult to place this. I have once seen a case of Gougerot's syndrome associated with a slightly enlarged spleen but I think it must be most unusual. I was interested in the observation that steroids were apparently not of much use here. In another case I found that repeated courses of steroids unequivocally failed to improve the condition.' This patient had from time to time a drop in her platelet count.

Auriculotemporal Syndrome.—M. FEIWEL, M.R.C.P.

S. H., boy, aged 8.

History.—For about one year has suffered from attacks of flushing extending over the right cheek which come on while eating (meat, chocolate, fruit, cheese, &c.). Erythema appears one or two minutes after chewing and lasts for five minutes after eating has stopped. The mother recalls that the boy received a smack on the cheek prior to the onset of these attacks.

Clinical findings.—Normal skin. A flush appears on the right cheek while he is chewing an apple. There is no visible sweating. Normal on general physical examination.

Investigations.—Skull X-ray and barium swallow normal.

Comment.—The auriculotemporal syndrome, Frey's syndrome (Frey, 1923; Langenskiöld, 1946) has received recent attention (Glaister *et al.*, 1958). Sweating, sometimes accompanied by vasodilatation, appears in the cutaneous distribution of the auriculotemporal nerve during eating and usually follows operations on or infections of the parotid gland. The afferent pathway to salivary secretion lies in the glossopharyngeal nerve; the efferent parasympathetic secretory stimulus originates from the upper part of the medulla, leaves in the glossopharyngeal nerve, passes via its tympanic branch and the superficial petrosal nerve through the foramen ovale to the otic ganglion. Thence post-ganglionic fibres join the auriculotemporal nerve from which branches pass to the parotid gland. Glaister *et al.* suggest that, following injury, regenerating parasympathetic fibres destined for the parotid gland pass into neurilemma sheaths of degenerated sympathetic nerves. Thus secretory stimuli meant for the parotid gland pass to cutaneous sweat glands normally innervated by the sympathetic. Conversely, sympathetic fibres might come to innervate the parotid. Bloor (1958) would place the area of aberrant axonal regeneration in the neighbourhood of the perivascular sympathetic plexus of the external carotid artery and its branches, rather than within the auriculotemporal nerve trunk. There sympathetic nerves would lie near parasympathetic nerve filaments passing from the auriculotemporal nerve to supply the parotid gland. Our patient features gustatory vasodilatation rather than sweating. Cholinergic vasodilator fibres would appear to supply the skin vessels along the pathways of adrenergic sympathetic vasoconstrictor fibres. This explanation presupposes that the damage produced by a smack was sufficient to cause nerve degeneration. As the condition causes little disability no attempt at therapy has been made. In any case no promising line suggests itself.

REFERENCES

BLOOR, K. (1958) *Brit. med. J.*, ii, 1295.
GLAISTER, D. H., HEARNSHAW, J. R., HEFFRON, P. F., PECK, A. W., and PATEY, D. H. (1958) *Brit. med. J.*, ii, 942.
FREY, L. (1923) *Rev. neurol.*, **2**, 97.
LANGENSKIÖLD, A. (1946) *Acta chir. scand.*, **93**, 294.

The following cases were also shown:

Nævus Lipomatosus Subepidermalis.—Dr. STANLEY R. WOOD.

Multiple Skin Necroses (Arteriolar).—Dr. J. SAVAGE.

Bullous Pemphigoid and Psoriasis.—Dr. J. D. EVERALL (for Dr. G. B. MITCHELL-HEGGS).

(1) **Pigmented Lichenoid Eruption of Calves Following Prolonged Hypostasis.** (2) **Dermatomyositis and Carcinoma of Breast.**—Dr. BRIAN RUSSELL.

Darier's Disease.—Dr. J. S. PEGUM.

(1) **Epidermolysis Bullosa Dystrophica.** (2) **Epidermolysis Bullosa (Variant of Weber and Cockayne).**—Dr. C. M. RIDLEY.

Ichthyosiform Erythroderma (Brocq).—Dr. W. FRAIN-BELL (for Dr. G. B. MITCHELL-HEGGS).

Primary Tuberculous Complex of Skin.—Dr. J. M. GOGGIN (for Mr. M. HARMER and Dr. M. FEIWEL).

A girl, aged 8, who grazed her right elbow 4 months previously and now has an indolent lesion on the extensor aspect of the right elbow and a mass of matted softish glands, discharging through the skin, in the right axilla. She is on chemotherapy.

Case for Diagnosis, ? Lichen Planus, ? Leukoplakia.—Dr. M. FEIWEL.

A man, aged 31, who presents three years' persistent, irritating hyperkeratotic patches on either side of the natal cleft. Clinically or histologically the diagnosis of lichen planus is not definite and a pre-malignant condition cannot be excluded.

Case for Diagnosis, ? Lichen Nitidus.—Dr. W. FRAIN-BELL (for Dr. R. T. BRAIN).

Meeting
November 20, 1958

? Ergotism.—B. BENTLEY PHILLIPS, M.D.

D. K., female, aged 35. Housewife.

History.—Suffers from migraine. At the end of June 1958 she had migraine and took 5 tablets (small, white ones—composition unknown). Next day felt ill, developed large blisters on left arm and hand, then on knees and buttocks, and soreness of eyes and ulcers in the mouth. She was first seen by me on July 20, 1958, when she had a deep gangrenous ulcer of the buttock, about 3 in. deep and 1 in. in diameter, and smaller, healing ulcers of the right heel, right foot and left hand.

Clinical findings.—All the lesions have now healed with scarring. There is a depressed scar where the ulcer of the buttock has healed. There is limitation of movement, coldness and "Raynaud-like" appearance of left index finger.

Investigation.—Urine normal. Chest X-ray normal. Swab of ulcer: Coliform organisms, *B. proteus*; no fungus, no acid-fast bacilli. Full blood count normal. Kahn and Wassermann reactions negative. E.S.R. 26 mm. in one hour (Westergren). P.C.V. 36%.

Comment.—The unknown tablets were probably ergotamine tartrate, ? 1 mg. per tablet, this large dose causing arterial spasm and thrombosis of arterioles and small arteries, producing gangrene.

Leukæmia Cutis.—P. J. FEENY, M.D.

Mrs. B. K., aged 69.

The condition started eleven months ago on the limbs as an eruption of discrete, bright-red nodules which bled easily. It has been slowly progressive, causing some smarting and burning sensation but little itching. The nodules are now 0·5 cm. in diameter, reddish-purple and present in large numbers on the extensor surfaces of the upper limbs, backs of the hands, abdomen, back, lower limbs and in lesser number on the chest. The face, neck, palms and soles are not affected. Some of the nodules have become aggregated into dry, brown, flat plaques.

The patient had not been taking drugs.

Previous history.—Splenectomy (January 1948): A very large cyst of the spleen containing 2–3 pints of blood-stained fluid was found.

Investigations.—W.R. and Kahn negative. Chest X-ray normal. Urine: consistently a trace of protein.

Skin biopsies.—28.4.58: No infiltrate. 3.10.58: Dermal foci of myeloid cells, not diagnostic.

Sternal marrow smears.—25.3.58 and 16.9.58: Excess of platelets, not diagnostic.

Serial blood examinations.—An anæmia is present and there has not been much variation. It has been refractory to liver and iron.

R.B.C. 2,500,000; platelets 500,000 to 1,250,000. Hb 51% to 58% (6·25 to 7·5 grams %). W.B.C. has slowly risen from 22,500 to 58,000, and the earlier differential counts did not suggest a leukæmia, the proportions of polymorphs, lymphocytes and other cells being normal; the platelets, however, were grossly abnormal in appearance and many of them were excessively large. But on 26.8.58, when the total W.B.C. was 38,000, the differential count was myelos. 8%, metamyelos. 13%, stab cells 27%, polys. 25%, lymphos. 23%, monos. 4%.

This leukæmic transition was more evident on 12.11.58 when the total W.B.C. was 58,000 and the differential count showed: blast cells 5%, promyelos. 7%, myelos. 10%, polys. 63%, lymphos. 12%, monos. 3%.

Biochemistry.—Total serum protein normal, gamma globulin 34%, A/G ratio 3 : 4. Liver function tests normal. Blood urea normal.

Physical examination.—No glands palpable and no leukæmic deposits in the ocular fundi.

Treatment.—(1) March 1958: No response to three weeks' treatment with prednisolone, 25 to 15 mg. daily. (2) May 1958: No response to superficial radiotherapy (200 to 400 r given over a week to the affected areas on the limbs). Dr. H. C. Sims, the radiotherapist, considered that there should have been some response if the condition were at this stage a true leukæmia. (3) Blood transfusions are being deferred until the hæmoglobin falls to about the 40% level.

Comment.—At the hospital we consider that a myeloid leukæmia has been developing in this patient and that the next marrow smear and skin biopsy will emphasize this development.

POSTSCRIPT.—Marrow smear (3.12.58): about one-third of the cells were primitive members of the leucogenic series. Skin biopsy (4.12.58) showed a widespread pleomorphic cellular infiltrate of the dermis.—P. J. F.

(*Meeting to be continued*)

PARABAL

Reduces phenobarbitone intake to one sixth without loss of sedation.

50 tablets cost 2/3d. basic N.H.S.

Each tablet contains 260 mg. Phenobarbitone Sodium Dihydroxyaluminiumaminoacetate.

Samples and literature on request.

United Services Section

President—Air Marshal Sir HAROLD WHITTINGHAM, K.C.B., K.B.E., F.R.C.P.

Meeting
December 4, 1958

SYMPOSIUM ON ARTHROPOD-BORNE AND OTHER FORMS OF ENCEPHALITIS IN THE TROPICS

Major-General W. D. Hughes:

General Clinical Aspects

The clinical picture of encephalitis, which merely denotes an inflammatory condition of the brain, may present with a wide variety of signs and symptoms depending on the severity of the infection and on the localization of inflammatory lesions in one or other regions of the brain. The condition should be suspected in any non-specific febrile illness occurring in an encephalitic area, or in any case of aseptic meningitis. The typical case is easier to diagnose in the presence of other cases although there are numerous pitfalls. The disease is ushered in by fever, usually very high, this, plus severe headache, being the most prominent symptom. Numerous investigations for malaria and other tropical disorders are usually carried out at this stage. In two to three days this phase is succeeded by the acute encephalitis stage—the patient is severely ill with a high temperature and neck stiffness. More often than not he is lethargic, withdrawn and uncommunicative, but in some forms he may be irritable or violent. The head and neck and sometimes the upper part of the trunk are flushed and congested. The face is expressionless, the speech slow, thick and difficult to understand.

Then follows increasing evidence of general and focal brain damage such as convulsions, coma and paralysis. Pyramidal involvement is shown by spastic weakness, often unilateral. Bulbar involvement is not common but may show as facial weakness, nerve deafness, or difficulty in speech, and swallowing. Unlike encephalitis lethargica, disorders of eye movements and pupillary reactions are infrequent. Involvement of the anterior horn cells producing flaccid paralysis akin to poliomyelitis and affecting particularly the neck and shoulder girdle muscles is a feature of Russian spring–summer encephalitis. Extrapyramidal lesions may occur either in the cerebellum or basal ganglia; the latter are frequent, causing choreoathetotic movements. The course of the severe case is unpredictable, coma is a bad prognostic sign, but even the severe case may proceed to recovery.

Examination of the blood shows a raised erythrocyte sedimentation rate and an almost constant polymorphonuclear leucocystosis of moderate degree from 10,000 to 20,000 cells per c. mm. The cerebrospinal fluid usually shows a raised cell count of 100 to 200, polymorphic at first, but later predominantly lymphocytic. The protein content averages 50 to 100 mg.%, the sugar and chlorides remain normal.

The encephalitic stage has to be differentiated from infections with arbor viruses which are not primarily neurotropic, but may occasionally become so, such as those of dengue and West Nile fever, and from non-arbor virus infections such as polioencephalitis, aseptic meningitis, and post-infective encephalitis following chickenpox, measles, mumps, whooping-cough and vaccinia.

Bacterial infections such as tuberculous, meningococcal or pneumococcal meningitis; protozoal infections such as cerebral malaria and trypanosomiasis; spirochætal infections such as leptospirosis and syphilis and helminthic infections such as trichinosis may also have to be considered under certain circumstances.

There are also non-infective conditions producing paralysis, convulsions and coma, such as epilepsy, brain tumour, diabetes, trauma, poisoning, heat-stroke, hypoglycæmia and hysteria; and finally acute psychotic states with retardation and flattening of affect on the one hand, and excitement and mania on the other, may simulate certain aspects of the acute encephalitic.

With regard to treatment, there is no specific remedy, but good supportive measures can help considerably to reduce the mortality.

Lt.-Col. M. M. Lewis, R.A.M.C.:

General Epidemiology and Prevention

We are considering a group of zoonoses having a widespread reservoir in mammals and birds, and normally requiring an arthropod vector at some stage. Man is not a maintaining host for the viruses concerned; he is merely an incidental host. As explained by Audy (1958) with reference to all zoonoses, ". . . a pathogen exists unknown to man until he happens to intrude into the niche occupied by it". This brings me to my first point of particular interest to the military

hygienist. We cannot assess the military importance of arthropod-borne virus encephalitis by merely taking note of the number of overt and recognized human cases; if we did so we might underestimate the importance of these diseases to military communities.

There is serological evidence that these viruses are more widely experienced by man than was formerly supposed. Our recent appreciation of this fact may be compared with present-day understanding of the wide distribution of the poliovirus in the rural tropics. We now recognize the importance of poliomyelitis as a hazard to troops serving in the tropics; it is suggested that arbor virus encephalitis should be considered in a somewhat similar light.

Danger lies in the immigration of a large number of susceptibles to an enzootic area. This was how scrub typhus emerged from comparative obscurity to become an important cause of military man-power loss in World War II. *Rickettsia orientalis* flourished in Burma almost unknown until the arrival of large numbers of susceptibles in the shape of the 14th Army.

It is evident that "inapparent infections" with arbor viruses occur but, as yet, we do not know their true incidence. It may be presumed that there have been many cases among soldiers in the past, perhaps labelled "pyrexia of unknown origin", that were unrecognized infections with these viruses. This potential threat to the health of troops is almost world-wide. In the Far East the important virus is that of Japanese B encephalitis, which has caused serious epidemics in China and Japan. Our troops have had experience of this disease in Hong Kong and Malaya where, among the indigenous peoples, it is seen mainly to affect young children. In Europeans it affects all age groups. The virus has been isolated from two species of mosquitoes in nature, namely *Culex tritæniorrhynchus* and *Culex pipiens*. No sylvatic reservoir has yet been identified, although pigs and horses have been found naturally infected. In Singapore the disease has an "island" type of distribution which, as one would expect with what is primarily a zoonosis, is not related to concentrations of human population. A positive correlation with high rodent infestations, having a high parasitization index for trombiculid mites, has been noted by Dowling (1956) and others. However, the virus has not yet been demonstrated in either rodents or mites. Investigations by a Royal Army Medical Corps team in Singapore are continuing.

In the U.S.S.R. and some adjacent countries there is the virus of Russian spring–summer encephalitis, with a reservoir in woodland mammals and birds. The vectors are ticks of the family ixodidæ which transmit the virus to domestic animals as well as man. Infection through the ingestion of goat's milk also occurs. Although this virus was identified as recently as 1937 it is thought to be a very old disease. Allied to it is the virus of louping ill which affects sheep in Scotland and is of veterinary importance only. A closely related disease was identified in India in 1957 and named Kyasanur Forest disease. This virus has a natural reservoir among small rodents and is transmitted by ticks of the family ixodidæ. The 1957 epidemic was preceded by an epizootic among monkeys, large numbers of which were found dead in the forest (Work, 1958). One is reminded of the epidemiology of jungle yellow fever in Trinidad; it was in 1914 that Balfour reported the local negro saying that prior to an epidemic of yellow fever the red howler monkeys were to be found dead and dying in the high woods.

In the Americas there are the equine encephalitides—eastern, western and Venezuelan—and also St. Louis encephalitis. All four viruses are found in horses and birds, and cause encephalitis in man. Transmission is by culicine and aedes mosquitoes; bird mites have been found naturally infected with the virus of western equine encephalitis. In Africa there is the West Nile virus, possibly extending into the Mediterranean, and also other viruses such as the Semliki Forest and Bunyamwera viruses. Finally, in the Antipodes the arbor viruses are represented by the virus of Murray Valley encephalitis.

At first sight the extent of the military hazard which these arbor virus encephalitides represent may not seem very great; in Malaya only one European case of Japanese B encephalitis was reported in 1958 up to October 10. However, we shall not know the true incidence until special laboratory diagnostic services are readily available. Although there is already evidence of a wide distribution of these viruses in nature, there are many gaps in our knowledge regarding hosts and vectors. In addition, there is always the possibility that these viruses may become associated with urban vectors in a manner similar to yellow fever.

Therefore we must take note of the fact that a force of European troops might suffer a high attack rate if introduced into an enzootic area. A more detailed appreciation of the problem cannot be made until the gaps in our knowledge are closed. In this connexion medical intelligence, based upon surveys and research performed under peacetime conditions, is vital.

For prevention one would hope for vaccines as effective as the 17D yellow fever vaccine; with such protection troops and their commanders

would have little to fear from these viruses. Other measures include:

(1) Avoidance of enzootic and endemic areas, whenever possible.

(2) Vector control, which presents particular problems because usually the vectors are, as far as is known, not house-haunting species of arthropods, therefore kills of adult arthropods out of doors have to be attempted; to this end, dieldrin dispersed by swing-fog techniques has been used against culicines in Malaya with apparent success.

(3) Protection against the bites of arthropods by means of suitable clothing and repellents.

(4) Destruction of animal reservoirs may be considered. Yet one must proceed with caution because these maintaining hosts divert the disease away from man.

REFERENCES

AUDY, J. R. (1958) *Trans. R. Soc. trop. Med. Hyg.*, **52**, 308.
BALFOUR, A. (1914) *Lancet*, i, 1176.
DOWLING, M. A. C. (1956) Unpublished reports.
WORK, T. H. (1958) *J. Indian med. Ass.*, **31**, 111.

Colonel P. L. E. Wood:

Japanese B Encephalitis in the Far East

Between 1871 and 1935 some 15 epidemics of summer encephalitis were reported in Japan. Of these, 2 are of particular importance—those of 1924 and 1935. The 1924 epidemic spread through a wide area with its heaviest concentration round the Inland Sea, where the disease has remained endemic. Lewis *et al.* (1947) quote Japanese authorities who state that the disease claimed a 60% mortality among 6,000 cases. It was through clinical observations made of this epidemic that the disease was distinguished from Type A encephalitis and gained its name as Type B Japanese encephalitis. During the period 1924 to 1937 outbreaks occurred annually with a total of 21,300 cases over the entire period. The first successful virus isolation by monkey inoculation from the brain of a fatal case was made in 1934 by Hayashi. Subsequent studies were facilitated by finding in 1935 that the mouse was susceptible. St. Louis type encephalitis was first reported in 1933—occurring in the late summer. Boyd (1958) states that the clinical and pathological pictures of the 1924 Japanese and the 1933 St. Louis cases were identical. Serological differences were established later.

EPIDEMIOLOGY

In 1937 Inada, in Japan, was able to transmit encephalitis to mice by bites from a pool of naturally infected culicines. The Russians confirmed this work in 1940. Whereas laboratory-infected culicine and aedes mosquitoes have been proved capable of transmitting encephalitis virus to mice, and the list of sub-species capable of doing so is a growing one, isolation of the virus from mosquitoes infected in the natural state is limited to two, or possibly three, sub-species, and the record of failures to achieve isolation from large catches in the presence of epidemics is impressive.

The serological pattern in animals and birds has been studied in Japan, in Okinawa in 1945 by Sabin (1947) and in Malaya by Paterson *et al.* in 1952. Between 1941 and 1943, Mitamura *et al.* (1950) carried out a serological survey embracing Korea, Manchuria, Central China, Indo-China, Hainan, and Java. They found inhibitor substances present in sera from 95% of a large selection of horses in Japan. While there was no evidence of the St. Louis virus in Japan, 7 out of 15 horses were thought to be positive to this virus in Korea. A parallel study on humans showed that experience of Japanese B infection varied widely in Manchuria, reached a high level, 65% positives, in Hangchoo in Central China and was 44% in Indo-China. Curiously enough there was no evidence of the virus on Hainan Island. Nowhere in the Far East did the survey reveal evidence of western equine encephalitis or louping ill.

Epizootics have only been recorded in horses in Japan in 1947 and 1948, and Singapore in 1951 (Paterson *et al.*, 1952). Virus strains isolated from horses in Japan in 1947 were shown to be similar but not identical with the Nakayama strain Japanese B virus (Tigertt *et al.*, 1950). Paterson *et al.* (1952) examined convalescent sera from 7 race-horses recovering from encephalitis in Singapore. They demonstrated significant levels of neutralizing antibodies to the Japanese B virus. These horses had been recently imported prior to their illness. American observers in Korea, Japan, Okinawa and Guam have all failed to find an epizootic running either a parallel or an antecedent course to the observed epidemic (Sabin, 1947; Tigertt *et al.*, 1950).

Kitaoka and Miura (1949), reporting on 72 human cases of Japanese B encephalitis in Okayama Prefecture in Japan between August and October 1947, pointed out that while an epizootic was widespread at that time throughout Japan only 6 cases of clinical disease among horses occurred in their prefecture. They stated that the morbidity rate in horses was at least a hundred times that in man.

Is summer encephalitis a fair synonym for Japanese B encephalitis? From 1939 onwards outbreaks of this disease, serologically, have occurred in Japan, Okinawa, Korea, Chunking and Peking, and Hong Kong, only in the summer

months. Climatically these countries enjoy a distinct summer, the rainy season, and winter. Mosquito breeding is limited to the summer. The Malayan climate shows no seasonal variations and, as one might expect, cases of Japanese B encephalitis have been shown to occur throughout the year (Morrison, 1958).

Where then does the virus live in the winter? A transovarian cycle in an avian or mammalian parasite, as has been demonstrated in western equine encephalitis, has not so far been discovered. Sabin (1947) summarized his extensive research on Okinawa when he stated that he had been unable to find either a mite host, a vertebrate host, or natural infection in a mosquito.

The Japanese have always recognized that the disease was primarily one of children. Sabin (1947), when investigating the endemicity on Okinawa, found that antibodies were present in 90% of sera from the over-20 age group and in 55% from the over-10's. About 90% of the adult civilian population of Singapore have neutralizing antibodies in their sera according to Morrison (1958). Lewis *et al.* (1947) noted that in Okinawa in 1945, out of 66 patients admitted with Japanese B encephalitis in that year's outbreak, 28 were in the age group 5 to 9, while 50 of the patients were under the age of 16. In a July outbreak in Chungking in 1944, 75% of cases were under the age of 10 (Chen and Chang, 1948). Hullinghorst *et al.* (1951), describing the 1949 Korean epidemic, stated that out of 5,000 cases reported over 60% were children between the ages of 2 and 12. The phenomenon of the "inapparent infection" has been studied in a small group of native school children, on Okinawa, by Blender and Cousins (1950). These investigators examined sera in March and again in September 1948 from the group. They found that 5 children with no demonstrable antibodies in March had developed them in September and this in the presence of only one single case of encephalitis in the district throughout the period. These children had remained perfectly well.

In the years 1945–1949 Sabin, quoted by Tigertt *et al.* (1950), noted the absence of serological evidence of the mild case on Okinawa. Sabin commented: "That this should obtain in spite of serological evidence of 'inapparent' infection in both Americans and native Okinawans strongly supports the hypothesis that such immune reactions are obtained without significant quantities of the virus becoming established in the brain, and that the virus, if once established in nerve tissue, usually multiplies to an extent sufficient to produce definite clinical disease. Mild clinical cases have been missed, but a strenuous effort has been expended without the recognition of any such cases in the entire Far East."

Here then is an endemic disease widespread throughout the Far East, characteristically producing sporadic, summer, outbreaks outside the tropics, which mainly affect children. There are big gaps in our knowledge of the part played by mosquitoes, or other arthropods, birds, mammals, and man in the spread of infection.

Incidence

There are several accounts of outbreaks of Japanese B encephalitis since 1945. Lincoln and Silvertson (1952) described the acute phase of the disease as they saw it in an evacuation hospital in Korea in 1950 where they handled 201 cases in U.S. troops. Lewis *et al.* (1947) reviewed the findings in a group of 66 patients admitted to a military government hospital in 1945. Tigertt *et al.* (1950) included Lewis's cases in their review of 401 cases on Okinawa between 1945 and 1949. Of this total only 21 were American soldiers. Edgren *et al.* (1958) have described 54 cases of encephalitis from a simultaneous epidemic of mumps and Japanese B encephalitis which they witnessed on Guam in 1947–8. Pieper and Kurland (1958) followed up most of these cases ten years later, in 1957, and were able to report on the sequelæ. Dickerson *et al.* (1952) discussed the diagnosis and immediate prognosis basing their observations on more than 200 patients with a detailed analysis of 65 serologically confirmed ones. Dickerson's cases were American soldiers from Korea, whom he saw in a base hospital in Japan, many of whom had been seen initially and described by Lincoln and Silvertson (1952).

Hong Kong's contribution is some 20 cases among British soldiers seen in 1954, 1955 and 1958 by Bagshaw and Wood (1958). Chen and Chang (1948) gave an interesting account of an outbreak of summer encephalitis in Chungking in 1944 involving 40 patients, of whom 75% were children. Unlike any of the studies I have selected for mention they were unable to secure serological confirmation that their cases were in fact Japanese B encephalitics.

Morrison (1958) in Singapore has investigated 157 cases of acute infection of the central nervous system, excluding cases of poliomyelitis, between 1956 and 1958. The volume of serological work undertaken by the American medical research team at Kuala Lumpur working in conjunction with the R.A.M.C. has been great. In a preliminary report Morrison has stated that cases of proven Japanese B encephalitis may present with meningeal reaction only. Of his first 100 non-fatal cases the largest group, 18 cases, had a serologically proven Japanese B

infection and of these 7 patients had an aseptic meningitis only. He was left with an unexplained ætiology for 75% of his cases.

Tigertt *et al.* (1950) in their survey of three outbreaks involving 54 cases were only able to confirm the diagnosis serologically in 16. Edgren *et al.* (1958) mention 6 uncertain cases out of 48 cases of encephalitis. Lewis *et al.* (1947), using the complement-fixation test only, were able to confirm the diagnosis of Japanese B encephalitis in 88% of their cases. Bagshaw was only able to secure confirmation in 50% of his cases. As he remarks, patients lying in adjacent beds may have identical clinical appearances but different serology.

Clinical Course

The onset is usually acute, fever and severe headache disabling the patient in a matter of hours. Lincoln and Silvertson (1952) recognized three types of onset; a gradual one with a headache and low fever which might either terminate after four to five days or progress to a severe illness; an acute type with relentless headache, chills, vomiting and developing neck rigidity; and a hyperacute onset characterized by mounting fever, psychotic behaviour, and fits. They were able to recognize the cases on screening by their facies, by the flushed faces, blank staring eyes, and injected conjunctivæ. They were seeing all their cases within forty-eight hours of onset. Headache was a constant finding, nuchal rigidity could be demonstrated in 90%. Half their patients were vomiting while an aching of muscles combined with a "weakness" in performing movements was seen in 25%. Only 14% complained of diplopia and blurring of vision.

By the third or fourth day of the disease they had noticed deterioration of behaviour in 70% of cases. Marked confusion, violent and irrational behaviour, irritability, release of inhibitions and lack of sphincter control were features. They stated that lysis might occur as early as the fourth and as late as the eleventh day and that with lysis the patient might make a dramatic improvement—becoming rational and co-operative overnight. The state of the superficial reflexes was related to the sensorial change, if present. 69 patients (34%) had complete loss of abdominal reflexes and 91% of these showed sensorial changes. They considered that a return of these reflexes early in lysis might precede mental improvement and constitute a valuable prognostic sign. With other observers they commented on the unpredictable nature of the tendon reflexes, varying from day to day. Paralyses were upper or lower motor neuronal in type. There was a flaccid paralysis in 7% of their series.

Chen and Chang (1948) described 5 out of 40 cases with unilateral or bilateral spastic paralyses. 23 of Lewis's 66 cases showed transient or persistent paralyses (Lewis *et al.*, 1947). Transient mono- or hemiplegia was seen in 11, and VII nerve pareses in 2. Rigidity of varying degree is fairly common and this may be limited to one limb.

Tremor of the tongue, dysarthria, and gross slurring of the speech are all common signs in varying degrees of severity. A typical aphasia with a right-sided hemiplegia was seen in one of Lewis's cases. He remarked that the pupils were frequently contracted and fixed. He noted dissociated eye movements and nystagmus in 7 patients, and recorded trismus, athetoid positions, and excessive salivation as less common signs. Fever progressing to hyperpyrexia, deepening coma, and loss of reflexes accompanying coma were bad prognostic signs. There was no relationship between the occurrence of convulsions and the ultimate outcome. There were 13 deaths among his 66 cases. 9 of these patients died within fifteen days of onset. He makes the interesting comment that the opinion held on the role of complications in North American encephalitis, that deaths occurring after four or five days are almost invariably due to complications, did not seem to hold in his cases since 4 of his patients dying after an illness of seven days or more showed no disease other than in the central nervous system. 3 of these cases appear to have been in coma for more than thirty-four days.

Tigertt *et al.* (1950) noted that 35% of 401 Okinawan and 28% of 21 American cases died between 1945 and 1949. Lincoln and Silvertson (1952) lost 17 out of 201 patients, a mortality of 8·5%, but this rate refers only to experience before the patients were evacuated—usually in the second week. Edgren *et al.* (1958) lost 4 out of 31 cases. Of 157 civil and military cases seen between 1956 and 1958, of which only a proportion were proven Japanese B infections, Morrison (1958) records that 36 died. A mortality of about 15% might be expected among Europeans, enjoying the advantages of good nursing.

Pathology

Haymaker and Sabin (1947) described the topographical distribution of lesions of the central nervous system in a detailed study of a patient who had died after a ten-day illness, the virus being recovered from the brain. They drew attention to the striking involvement of the grey matter, the relative sparing of the white matter, and the absence of change in the thoracic and abdominal viscera. The structures most severely affected were the substantia nigra,

thalamus, basal nucleus and anterior horns of the spinal cord. In these areas the lesions, which they identify as neuronophagic nodules composed of mononuclear cells, were confluent; while in the cerebral cortex and cerebellum the lesions were discrete.

Zimmerman (1946) examined the nervous systems and other viscera from 11 serologically proven cases in 1945. 9 of these cases were Okinawans and 2 were Americans. The duration of illness had ranged from five to thirteen days in 8 cases, and from thirty-seven to fifty-two days in 3. The histo-pathological changes were unlike those of post-vaccinal and the post-infectious encephalitides. In the latter, the lesions were confined almost exclusively to the central white matter of the brain and the fibre tracts of the spinal cord. They were almost always perivascular in distribution and consisted essentially of a breakdown of the medullary sheaths, accompanied by monocytic inflammatory changes. The white matter was spared except in those rare instances where the lesions spread from an affected collection of ganglion cells to encroach on the myelinated fibres. He regards the disease primarily as one of injury to ganglion cells with secondary inflammatory and regressive glial changes. Certain of its more distinctive features, such as the acellular plaques in the cerebral cortex and basal ganglia, the "spongy" lesions in the cerebellar cortex, and the deposition of calcium salts in the chronic cases, confer an individuality upon it, but it still resembles other forms of encephalitis of virus ætiology. He found typical bronchopneumonia of a non-interstitial type which was not suggestive of a virus ætiology in 3 cases.

Edgren *et al.* (1958) call attention to a case in which both the clinical and pathological findings at autopsy were indistinguishable from poliomyelitis; Japanese B virus was, however, isolated from the brain.

All observers agree on the laboratory findings. A total white cell count of between 15,000 and 20,000 with an increase in polymorphs is a common finding. Cell counts in the cerebrospinal fluid may vary from 10 to 1,000; a polymorph response may accompany the onset but the fluid is usually lymphocytic by the fifth day (Lewis *et al.*, 1947).

Lewis *et al.* (1947) found a raised protein—over 50 mg.%—in 12 out of 21 patients after the fifteenth day of illness and a dissociated raised cerebrospinal fluid protein has been noted by several observers. The sugar content remains normal.

Virus isolation from the cerebrospinal fluid was achieved *ante mortem* by Paterson *et al.* (1952). In this case the virus was also recovered from the brain at post-mortem and was named Kinrara '51 Strain.

Most observers agree that between 25% and 33% of all survivors will have clinical evidence of mental impairment or disturbed motor function on discharge.

Pieper and Kurland (1958) have recently published the results of a ten-year follow up of patients affected in the 1947–48 epidemic in Guam. They examined 23 out of 25 patients who had had serological evidence of Japanese B encephalitis with or without the probability of coincidental mumps infection and received reports on 2 others. 15 out of 25 had no sequelæ. Of the 8 who had neurological defects, in 3 a positive Babinski was the only evidence. 2 patients were mentally retarded. Sequelæ were more common in patients who were less than 10 years old at the time of the illness. They considered that there was a close correlation between the presence of convulsions and other signs of neuronal involvement during the illness, and the later development of sequelæ. Cerebrospinal fluid changes proved to be of no prognostic significance.

Diagnosis must depend on serological findings. Ideally a base-line serum taken as early as possible in the illness is examined for complement fixing, hæmagglutination-inhibition, and neutralizing antibodies. Serial sera are examined thereafter to show rises in titre.

Differential Diagnosis

The differential diagnosis mainly depends on the presence or absence of associated cases. The sporadic case when first seen is likely to present as a meningo-encephalitis. It seems logical to exclude as a matter of urgency those conditions for which specific therapy exists. Under this heading paratyphoid B, cerebral malaria, tuberculous meningitis, meningococcal meningitis, cerebral abscess, vascular accidents, and heat stroke are among the possibilities.

In the face of an epidemic the preliminary diagnosis of an arbor virus encephalitis may be relatively easy.

A more difficult differentiation is between this condition and polioencephalitis. The short sharp onset, the relative infrequency of cranial nerve pareses in Japanese B encephalitis, and the waxing and waning of various physical signs in this disease may help to distinguish the two conditions in the early stages. Lincoln and Silvertson (1952) never saw respiratory paralysis in any of their 200 cases and I can find no reference to this complication in any other reports. The post-infective and vaccinal encephalitides should usually be excluded on the history but Edgren *et al.* (1958) describe a simultaneous

outbreak of mumps and Japanese B encephalitis.

TREATMENT

No specific treatment has yet been discovered. The physician aims at nourishing the patient from the onset through what may prove to be a lengthy illness, in which high fever and extreme restlessness may combine to produce rapid loss of weight. He also has to avoid complications, the most serious being due to aspiration of food, vomit, or secretions. His role in preventing fits is less clear. Hyperpyrexia may develop early and is not necessarily a terminal event. It can be controlled.

I found an intragastric drip containing a complete food aimed at supplying 2,000–3,000 calories per day an easier technique to maintain in the face of delirium and violence than intravenous drips.

I feel sure that chlorpromazine has a definite sedative and probable anti-emetic effect in these cases and used it for up to seven days in four-hourly doses totalling up to 200 mg. per day in the drip.

My patients were nursed in air-conditioned wards—on a firm mattress, without pillows, loosely constrained by flannelette halters round wrists and ankles. Turning from side to side combined with percussion over the bases and head-tipping downwards to 10 degrees in the prone and lateral positions were carried out two-hourly. Rectal temperature, pulse and respiration records were charted two-hourly. Aspiration of pooled secretion was carried out frequently. A vomit was the signal for tipping the foot end of the bed up 25 degrees.

Equipment for performing tracheotomy under Pentothal anæsthesia following endotracheal intubation was at hand. Bagshaw (1955) was forced to do a tracheotomy to obtain an adequate airway on one patient.

I have omitted any references to prevention by mosquito control, segregation of troops from civilians, or vaccination. I have not included India in my survey but I should point out that a virus allied to the Japanese B virus was isolated from cases of encephalitis among children in Vellore in the autumn of 1955 (Indian Council of Medical Research, 1957). The Western boundary of the endemic area of South-East Asia remains indefinite.

REFERENCES

BAGSHAW, F. B., and WOOD, P. L. E. (1954–8) Unpublished reports.

BLENDER, J. X., and COUSINS, R. F. (1950) *vide* TIGERTT *et al.* (1950).

BOYD, W. (1958) Pathology for the Physician. 6th ed. London.

CHEN, K. T., and CHANG, H. H. (1948) *Chinese med. J.*, **66**, 409.

DICKERSON, R. B., NEWTON, J. R., and HANSEN, J. E. (1952) *Amer. J. Med.*, **12**, 277.

EDGREN, D. C., PALLADINO, V. S., and ARNOLD, A. (1958) *Amer. J. trop. Med. Hyg.*, **7**, 471.

HAYASHI, M. (1934) *Proc. Imp. Acad. Japan*, **10**, 41.

HAYMAKER, W., and SABIN, A. B. (1947) *Arch. Neurol. Psychiat., Chicago*, **57**, 678.

HULLINGHORST, R. L., BURNS, K. F., YOUNG, T., CHOI, M. D., and WHATLEY, L. R. (1951) *J. Amer. med. Ass.*, **145**, 460.

Indian Council of Medical Research (1957) A Review of Activities During the Years 1950–7. Calcutta.

KITAOKA, M., and MIURA, T. (1949) *Jap. med. J.*, **2**, 55.

LEWIS, L., *et al.* (1947) *Arch. Neurol. Psychiat., Chicago*, **57**, 430.

LINCOLN, A. F., and SILVERTSON, S. E. (1952) *J. Amer. med. Ass.*, **150**, 268.

MITAMURA, T., KITAOKA, M., and MIURA, T. (1950) *Jap. med. J.*, **3**, 257.

MORRISON, R. J. G. (1958) Unpublished reports.

PATERSON, P. Y., *et al.* (1952) *Amer. J. Hyg.*, **56**, 320.

PIEPER, S. J. L., JR., and KURLAND, L. T. (1958) *Amer. J. trop. Med. Hyg.*, **7**, 481.

SABIN, A. B. (1947) *J. Amer. med. Ass.*, **133**, 281.

TIGERTT, W. D., *et al.* (1950) *Amer. J. trop. Med.*, **30**, 689.

ZIMMERMAN, H. M. (1946) *Amer. J. Path.*, **22**, 965.

Lt.-Col. W. O'Brien, R.A.M.C.:

African Arthropod-borne Viruses

The subject of arthropod-borne neurotropic viruses would be incomplete without reference to some of the African arbor viruses. A brief survey of recent work on the subject seems appropriate.

Arbor viruses besides those of yellow fever and dengue have been shown to be widespread in Africa as well as Asia. Between 1937 and 1947 Dick and Smithburn in the course of yellow fever research at Entebbe discovered eight of these arbor viruses and since then new ones have been constantly added to the list (Dick, 1953; Smithburn, 1940). They have been given geographical and often unpronounceable names corresponding to the place at which they were first found, which place of first discovery often bears little relation to their general distribution. On the whole it seems that these African arbor viruses tend to be viscerotropic rather than neurotropic. At least some of them, however, do show neurotropic properties and whether they are likely to cause encephalitis is still uncertain. These arbor viruses have been classified by Clarke and Casals (1958) into groups depending upon the hæmagglutination reaction. In Africa there are representatives of all groups.

African group A viruses include Chikungunya, Middleberg, Semliki Forest and Sindbis viruses. The Chikungunya virus has been responsible for epidemics of an illness exactly resembling dengue in both Uganda and the Northern Transvaal (Robinson, 1955). The domestic *Aedes ægypti*

is the chief vector and it is possible that monkeys form a reservoir of infection. Infected monkeys develop encephalitis. Chikungunya is not a place name but translated means "that which bends up".

African group B viruses include yellow fever, dengue 1 and 2, Ntaya, Zika, Wesselbron, West Nile, and Uganda S viruses. The West Nile virus in many ways closely resembles the virus of Japanese B encephalitis. Serologically it is closely related; like Japanese B, epidemic spread of infection depends upon the primary infection of bird fledglings, notably the hooded crow (Work *et al.*, 1955). This infection gives a boost to mosquito infection, and these in turn infect man. Though this virus was first isolated by Smithburn from the blood of an African woman suffering from a mild fever in the West Nile region of Uganda, the maximal incidence of infection appears to be in Cairo where 70% of the population show significant antibodies in their blood. In Egypt the infection is seen chiefly in children, and produces a dengue-like illness, though this is often masked by malaria, as the season for both infections coincide. Epidemics of a dengue-like illness due to this virus have been reported from Israel in 1950, 1951 and 1952. In these outbreaks there were cases of aseptic meningitis with considerable pleocytosis in the C.S.F. (Bernkopf and Levine, 1952). Moreover, inoculation of this virus into patients suffering from cancer caused encephalitis in 9 out of 78 (Southam and Moore, 1954). The vector in Israel was the *Culex molestus*. Another virus of this group, the Zika virus carried by *Aedes africanus*, has been associated with outbreaks of hepatitis (Macnamara, 1954). This virus is highly neurotropic to mice following intraperitoneal inoculation. Antibodies to the Zika virus are widespread amongst the population of Eastern Nigeria.

Besides these there are other viruses so far ungrouped. The Bwamba fever virus first isolated, again by Smithburn, from the blood of immigrant labourers in Uganda is now thought to be one of the commonest causes of febrile illness in Central Africa and 80% of the inhabitants of Uganda show significant antibodies to this virus in their blood. It produces a mild fever lasting two to five days. The Bunyamwera virus, though as yet not associated with known naturally occurring infections in man, when experimentally inoculated into one man produced a nearly fatal encephalitis. The Rift Valley fever virus primarily infects cattle and sheep producing, like yellow fever, a mid-zonal necrosis of liver cells. Herdsmen and milkmen coming into contact with these animals are often infected. A sudden fever, rigors, a tendency to a saddle-back temperature chart, flushed face, severe body pains, Faget's sign and a sense of heaviness in the liver region make up a clinical syndrome not unlike that of yellow fever. Retinal complications with resultant loss of vision have been reported. *Aedes caballus* is an efficient vector but it is still doubtful whether human infections commonly occur through this agency.

The mengo-encephalitis virus has been associated with one definite case of encephalitis and several cases of aseptic meningitis. Though isolated from the *Culex tæniorrhynchus*, Dick, who incidentally developed encephalitis whilst working with the virus, doubts whether infection is mosquito-borne. Rats, monkeys and mongoose are also infected and infection in man may be due to accidental contamination of food by virus excreted in the urine and fæces of rats. This virus is related to the encephalomyocarditis virus.

It will be seen that these viruses are widespread throughout the African continent and that infections follow the clinical and epidemiological pattern of arbor virus infections. The clinical picture is that of a dengue-like illness on which may be superimposed hepatitis or encephalitis. Epidemiologically there are animal reservoirs and mosquito vectors. Where climatic conditions remain constant throughout the year infection is endemic and mostly confined to children. Where the climate shows seasonal variation epidemics occur. Though for the most part the nervous lesions have been mild or produced in rather unnatural circumstances, it would be unwise to regard these viruses as non-neurotropic. Arbor viruses are characteristically neurotropic. If encephalitis were to occur it would be mostly the children of the indigenous population who would be affected. With the very limited facilities available throughout these areas, the differentiation of such an illness from cerebral malaria or even tick typhus, relapsing fever, mumps and polioencephalitis, trypanosomiasis and toxoplasmosis is difficult. Anyone who has worked in Africa will have seen cases of encephalitis confirmed at autopsy as being of unknown cause. Such cases are particularly common in European children. So far attempts at virus isolation from the brains of these patients have been unsuccessful. Geerling (1950) in Johannesburg had collected 100 cases of acute encephalitis of unknown origin by 1950 and drew attention to the extremely high rate of post-encephalitic parkinsonism amongst Africans in Johannesburg. Basal ganglia disease is a good deal more common amongst Africans than Europeans. There has recently been described an outbreak of encephalitis amongst immigrants seeking diamonds in Sierre Leone (Rose, 1957).

Though no particular arbor-virus encephalitis has so far been recognized in Africa, it would be rash for those responsible for the introduction of large numbers of young non-immunes into such areas not to be at least conversant with the possibilities. It would be a strange thing if the continent of Africa where so many diseases are insect-borne should be the only continent where arbor-borne virus encephalitis did not occur.

REFERENCES

BERNKOPF, H., and LEVINE, S. (1952) *Bull. Res. Coun. Israel*, 2.

CLARKE, D. H., and CASALS, J. (1958) *Amer. J. trop. Med. Hyg.*, **7**, 561.

DICK, G. W. A. (1953) *Trans. R. Soc. trop. Med. Hyg.*, **46**, 13.

GEERLING, R. (1950) *S. Afr. med. J.*, **24**, 339.

MACNAMARA, F. N. (1954) *Trans. R. Soc. trop. Med. Hyg.*, **48**, 139.

ROBINSON, M. C. (1955) *Trans. R. Soc. trop. Med. Hyg.*, **49**, 28.

ROSE, J. R. (1957) *Lancet*, ii, 914.

SMITHBURN, K. C. (1940) *Amer. J. trop. Med.*, **20**, 471.

SOUTHAM, C. M., and MOORE, A. E. (1954) *Amer. J. trop. Med. Hyg.*, **3**, 19.

WORK, T. H., HURLPUT, H. S., and TAYLOR, R. M. (1955) *Amer. J. trop. Med. Hyg.*, **4**, 872.

Major V. M. Innes, Q.A.R.A.N.C.:

Nursing of Encephalitis

In the tropics, because of the long-term nature of this disease and the absence of any specific remedy, good supportive measures are necessary. Conditions such as hyperpyrexia, convulsions, etc., require very special treatment.

Nursing is specifically directed towards:

(1) *The maintenance of a free airway* and measures to prevent the inhalation of vomit. The patient is nursed on a firm mattress with no pillow, using a tipping bed or with foot of bed blocked. It is stressed that if the patient is kept in a lateral position, a clear airway can be maintained in conjunction with a strict regime of hourly tipping, turning and oral suction.

(2) *Adequate fluid and nutritional intake.*—During the first forty-eight hours of the unconscious or delirious stage fluids are given intravenously, followed on the third day by intragastric feeds through a Ryle's tube. Pre-checking the position of the tube and withdrawing and charting the residual gastric contents are necessary before each feed, emphasis being placed on the danger of a condition resembling paralytic ileus, and consequent inhalation of vomit. The twenty-four-hour diet comprises six pints of milk plus four ounces of Complan, a total calorific intake of 2,500. The patient's mental condition will determine whether continuous or intermittent feeds should be given.

(3) *Protection of violent cases* from injury by gentle restraint with the use of loose halters to wrists and ankles may be necessary should a delirious or obstreperous state ensue.

(4) *Urgent antipyrexial measures* are initiated by frequent tepid sponging, and in extreme cases by the careful use of fans and wet sheet cradling, in an endeavour to reduce the temperature to 103° F. or thereabouts.

(5) *The control of convulsions and prevention of bedsores.*—The Ryle's tube proves an adequate vehicle should heavy sedation be necessary, drugs usually given being chlorpromazine 75 mg. initially in conjunction with a maintenance dose of up to 200 mg. daily. Additionally phenobarbitone 2 grains daily is used with success. Convulsions occurring in patients not fed intragastrically may be controlled by the use of such sedatives as intramuscular paraldehyde 5 ml. to 10 ml. or soluble phenobarbitone 3 grains. Bedsores are prevented by careful moving and skin care, in conjunction with a high protein diet.

(6) *Observations of the patient.—Two-hourly recording of rectal temperature and blood pressure* is continued during the acute febrile stage and *the pulse and respiration rate are recorded every fifteen minutes*, emphasis being placed on the dangers of medullary involvement and the necessity of early recognition of change in the conscious state. It is essential that every member of the staff should readily appreciate any change in the patient's condition and be able to give detailed verbal and written reports of the patient's condition and treatment.

Conclusion.—From the Service point of view the moral to be drawn from this is that these measures call for the very highest standard of training among Army nursing personnel, as events may move with dramatic suddenness, and unless skilled and devoted observation is constantly available for each and every case, and unless every member of the nursing staff is capable of carrying out emergency forms of treatment such as clearing airways, regulating drips and reducing hyperpyrexia, tragedies will occur which should be preventable.

Lastly the point must be made that the nursing of patients in air-conditioned and mosquito-proofed surroundings is a first essential in the prevention of hyperpyrexia, which is often the ultimate cause of death, and of infection of further insect vectors which are responsible for the epidemic spread of the disease.

In areas such as Singapore, Malaya and Hong Kong therefore, where some of these viruses and their vectors are already known to exist, high priority should be given to these essentials in all Military hospitals and Static Medical Units.

Major R. J. C. Hart, R.A.M.C.:

Laboratory Investigations

Work's (1958) account of the discovery and investigation of Kyasanur Forest disease, due to a tick-borne virus related to Russian spring–summer encephalitis virus, shows how rapidly knowledge of a new virus in this group can be acquired by a highly-trained team.

The first step in the characterization of a disease entity is the isolation and identification of the virus from the patient. Isolation of arthropod-borne viruses is usually carried out in suckling mice and may be very easy or difficult, depending on the susceptibility of the animals to the virus and its concentration in the tissues examined. Identification of a virus may present serious difficulties, and involve numerous passages for the preparation of suitable antigens. The work of Casals and others (Clarke and Casals, 1958) on the classification of these viruses on the basis of the hæmagglutination-inhibition test has simplified this process, but the close antigenic relationships between many of the viruses in group B increase the difficulty of definitive classification of these viruses.

Having isolated a virus from a patient, it is desirable to prove that its presence has resulted in a specific antibody response. Three techniques are in use for examining patients' sera. The hæmagglutination-inhibition test is valuable in that antibody can be detected early, sometimes in about a week from the onset of the disease, but the specificity of the test is often too broad for it to be possible to determine precisely which virus is responsible. Antibody to the complement-fixation test develops later and is usually more specific. The neutralization test is the most specific but requires large numbers of mice. All of these tests have technical difficulties, and require careful standardization.

Serological surveys of the population of an area are conducted with a view to finding out which viruses are or have been infecting man in that area. The three tests already mentioned may all be used, but the lack of specificity often makes it impossible to be certain which viruses have been at work, although certain probabilities can be stated. Thus Hammon *et al.* (1958), conducting a serological survey in Manila, found antibodies which led them to suspect that the viruses of eastern equine, Japanese B encephalitis and dengue were present, together with at least one other virus from group A and two from group B. This type of investigation by itself is of limited value, but is an invaluable part of a larger study as it gives some indication of where the next moves lie.

These serological tests can also be used to discover antibodies in animals and birds in order to indicate the natural reservoirs of the diseases, and as a means of diagnosing experimental infection of an animal which survives.

Vectors can be investigated by attempts to isolate virus from them. Insects are trapped in various ways, and pools of insects are ground up and inoculated into suckling mice. Laboratory experiments with insects have also yielded valuable information as to their potential effectiveness as vectors when field information was not available.

Virus isolations from, and infection experiments in, animal and bird reservoirs are required to show their importance. Transmission experiments may also be necessary before the cycle of a virus can be completely elucidated, and points of attack at which it might be broken discovered.

Whilst this field work is in progress, the characters of the virus have to be investigated. One reason for this is the need for diagnostic tools—antigens, stable suspensions of virus, antisera prepared in animals and so on. The other reason is that the preparation of an effective vaccine should be an objective early in the study of such viruses.

Such a vaccine might be living or killed, grown in animals, eggs or tissue culture. In either case, the initial aim is to find a technique of growing virus uniformly to very high concentrations. The tissue in which it is grown must be non-toxic. If a live virus is used, it must be so attenuated as to cause no effects; while a killed one must contain no living organisms. The production of experimental vaccines has sometimes reached this stage and yet foundered because the material was not antigenically potent.

Only when the characteristics and life cycle of the virus are so well understood that preventive measures have achieved perfection is the virologist entitled to consider that his only task is the diagnosis of human disease, and by this time the disease should ideally have been wellnigh eradicated.

REFERENCES

CLARKE, D. H., and CASALS, J. (1958) *Amer. J. trop. Med. Hyg.*, **7**, 561.

HAMMON, W. McD., SCHRACK, W. D., and SATHER G. E. (1958) *Amer. J. trop. Med. Hyg.*, **7**, 323.

WORK, T. H. (1958) *Progr. med. Virol.*, **1**, 248.

Section of Neurology

President—HUGH GARLAND, T.D., M.D., F.R.C.P.

Meeting
November 6, 1958

DISCUSSION ON PSYCHOSURGERY

Dr. Alick Elithorn (London)[1]:

Prefrontal Leucotomy and Depression

The material on which this paper is based is a follow-up study of those patients who underwent a leucotomy operation at the National Hospital for Nervous Diseases, Queen Square, before June 1954, and who were seen and followed up by the Department of Psychological Medicine. In addition there are two patients who had a cingulectomy at Oxford by the late Sir Hugh Cairns.

This investigation was undertaken in collaboration with Dr. Eliot Slater and Mr. E. Glithero, while the author was a member of the Medical Research Council Neurological Research Unit, directed by Dr. E. A. Carmichael. It reports the results obtained with the 105 patients who completed the formal questionnaire. A detailed description of the methods used in this follow-up study has been published elsewhere (Elithorn *et al.*, 1958).

In addition to a clinical assessment each patient, and in almost all cases the nearest relative, was asked certain formal questions. Each patient was asked the same six questions:

(1) Whether the operation had helped him and, if so, how.

(2) Which symptoms had improved (or) had any symptoms improved.

(3) Which symptoms had not improved.

(4) Had he noticed any bad effects.

(5) Had he noticed any change in personality.

(6) Was he glad that he had had the operation, did he regret it, or was he undecided.

This last question was arranged as a five-point scale: if the patient was glad he was asked if he was very glad or just definitely glad; if he was sorry, whether he just regretted it or regarded it as a great mistake.

Previous studies of the effects of leucotomy have supported the thesis that there are two distinct types of depressive reaction—reactive and endogenous (Partridge, 1949; Pippard, 1956).

The concept of a specific neurogenic depressive illness determined partly by one or two genes of large effect is not only not accepted by the psychoanalytical schools but is incompatible with the statistical models put forward by Eysenck. Recently this concept has been rejected by Garmany (1958) on the basis of a clinical analysis. The present series is a small one, but it is of some interest to see whether the results support this thesis or not.

Depression and depressive illness are difficult to define. I have followed Partridge and Mapother in treating as depressive illnesses those states in which the depressive emotions have for the time being lost their direct relationship to current experiences and have achieved an autonomous existence, often determining secondary symptoms. Where the complaint of depression is realistic in relation to other symptoms or external stresses I have classified the complaint of depression as a symptom. In separating the possible endogenous illnesses from the reactive ones I have used not only the customary physiological criteria but have applied *Partridge's paradoxical principle*. This states that the illnesses most likely to be endogenous in origin are those which appear to have struck the patient from without and to be alien to his normal personality. In the reactive depressions not only did the more physiological symptoms tend to be absent but there was good evidence of environmental stress, either physical or psychological in character, and generally evidence of a poor personality organization.

In the present analysis the patients have been classified according to usual psychiatric diagnostic practice and independently according to the character of the depressive reaction present. The psychiatric diagnoses were as follows: manic-depressive disease, 9; involutional depression, 14; mixed depressions, 7; depressions reactive to an unpleasant stimulus (pain, tinnitus or abnormal movements), 28; obsessional neurosis, 16; schizophrenia, 6; anxiety states including anxiety hysteria, 14; hysteria, 1; hypochondriasis 7; organic dementia, 1; facial tic, 1;

[1]National Hospitals for Nervous Diseases and the Royal Free Hospital, Part-time Member of the Medical Research Council's External Staff.

anorexia nervosa, 1. This series is not of course a cross section of patients undergoing leucotomy and as might be expected it contains a high number of patients with an objective physical disability.

The depressive reactions in these patients were classified as follows: recurrent endogenous, 6; recurrent endogenous but with poor personality organization, 5; recurrent reactive with poor personality organization, 11; single endogenous, 21; single reactive, 24; depression only a symptom, 31. In 7 cases there was no complaint of depression. It is perhaps worth recording that of 24 of the patients who developed a reactive depressive illness in response to a physical disability 6 or one-quarter had had a previous depression.

Results

50 patients had a standard leucotomy; of these 44 (88%) were rated as improved, 6 (12%) as unimproved or worse, 38 (76%) replied positively to the question, "Has the operation helped you?" 12 (24%) denied improvement. Of the 55 patients treated by a modified operation, 43 (78%) were rated as improved, 12 (22%) as unimproved or worse. In this group, only 29 or 53% felt the operation had helped; 26 or 47% denied improvement. In 14 of the 105 cases both the clinical rating and the patient agreed that the operation had been a failure. In only 2 cases did both agree that the patient was worse.

Fig. 1 shows, for those patients who had a depressive reaction, a more detailed analysis of these results. The clinical rating is on a five-point scale. The patient's assessment is in terms of whether or not he felt glad that he had had the operation.

It is clear that the results are assessed as better with the patients who suffered from the endogenous type of depression, and that these patients are much more enthusiastic about the results of the treatment than are those who suffered from reactive depression. In the endogenous group 27 or 84% were glad that they had had the operation, in the reactive group only 18 or 51% were glad. Only one patient suffering from an endogenous illness regretted having a leucotomy. Of the reactive depressives 8 regretted the operation and 9 were neither glad nor sorry.

This result cannot be attributed to the fact that a greater proportion of the patients who suffered from an endogenous depression had a standard operation. In the reactive group, of 24 patients who had a modified leucotomy only 9 or 38% thought it worth while. Of the 15 patients with endogenous depression who had a modified

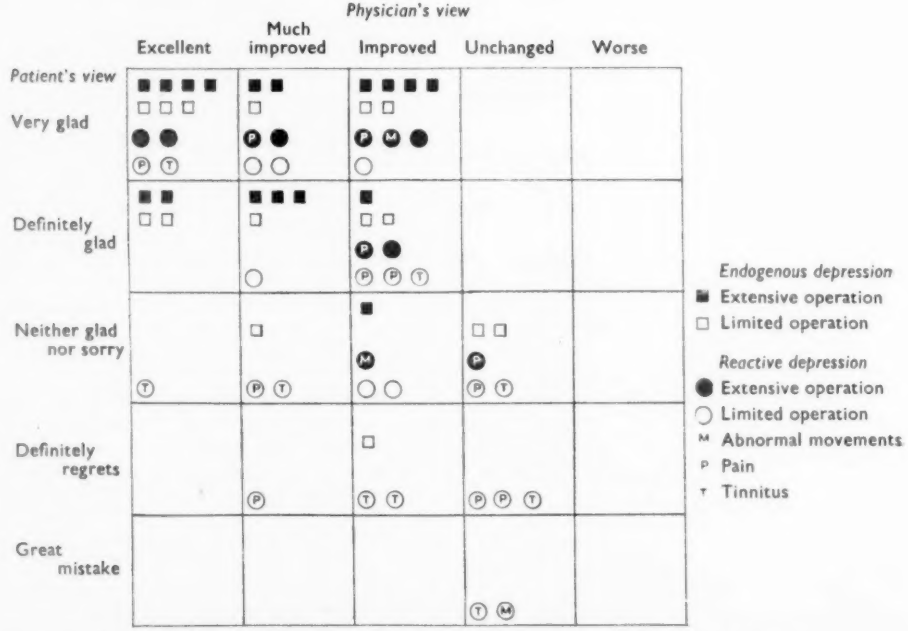


Fig. 1.—Relationship between each clinical assessment and that made by the patient.

operation 11 or 73%—nearly twice as many—were glad.

The results obtained in the reactive depressions were related to the type of environmental event which determined the illness. As a group, the 24 patients whose depression was clearly secondary to a definite physical disability were markedly dissatisfied with their operation; only 9, or 38%, were glad they had it. With the 11 patients whose depression seemed to be reactive to purely psychological events, the results are clearly much better—only 2 were not glad. Thus in the patients with reactive depression, really good results were obtained almost exclusively in the group in which there was least clearly a stressful external event.

This difference cannot be attributed to differences in the type of operation. The effect is present whichever type of operation is used, but is more marked with the modified operation. Here only 5 out of 18 in the pain, tinnitus and movement group are glad that they have had the operation; 4 out of 6 in the psychological group are glad.

Elithorn *et al.* (1958) have shown, in a separate analysis of the pain cases, that the more clearly there is a real and objective cause for reactive distress the less likely it is that the patient will be relieved by leucotomy. The results obtained in the reactive group as a whole confirm this observation. If, therefore, one regards endogenous depression merely as a type of reactive depression in which there is a minimal external valid and real cause for the distress, then the results obtained with leucotomy should be even better than they are with the reactive depressions. They should be best of all in those cases where there is least evidence of any external cause. I refer of course to the truly cyclical or manic-depressive cases. Both Partridge and Pippard have shown that this is not so and the present observations, although small in number, support their findings.

In the present series there are 9 undoubted manic-depressives. Of these 6 had relatively short cycles. In each case the depression has recurred post-operatively at about the expected date. Because of some attenuation of symptoms they have been classified as improved in 4 cases and much improved in 2. In the remaining 3 cases the intervals between depressive spells were so long that no recurrence could be expected within the follow-up period. One patient was operated on in her first endogenous depressive illness; this failed to produce improvement and she subsequently had a second leucotomy. Following this, and perhaps not because of this, she recovered and showed a very marked frontal lobe syndrome. She was, however, able to continue living at home and subsequently had two further depressive illnesses. She is at the present time suffering from her first manic attack. The other 2 cases had intervals of twelve and seventeen years between their attacks. Our results, therefore, though small in number, strongly support those who maintain that leucotomy fails to affect the enduring physical basis which underlies cyclical depressive illness. In our cases, as in those of other workers, the intensity or elaboration of the depressive spell was diminished.

So far I have discussed the effects of leucotomy in depressive illness and have concluded that it is less effective both where depression is most clearly autonomous and where it is reactive to a real disability. What is the effect of the operation in those patients in whom depression remains a symptom and does not develop into an autonomous state?

In those cases—the pain, tinnitus and movement group—in which the cause of the depressive complaint is most obviously unaffected by the operation, the results are unsatisfactory and in particular are not appreciated by the patient; 3 out of 10 were glad they had had the operation. In the psychiatric illnesses the results are better; 11 out of 17 being glad. These latter results largely reflect the effect of the operation on the primary illness.

As might be expected, the more extensive operation more readily abolishes a complaint of depression, but both standard and modified leucotomies tend to relieve depression more readily in those cases in which it has assumed an autonomous existence than in those in which it remains a symptom. Partridge, on the basis that leucotomy did not relieve many endogenous depressions, formulated the thesis that the operation relieves the "load" but not the affective loss. Pippard also relates favourable changes in energy output to the removal of hampering symptoms. The evidence of the present series does not support this view. As has been argued elsewhere (Elithorn *et al.*, 1958; Elithorn and Beck, 1955) leucotomy appears to have two main effects. Firstly, and this is widely admitted, it permanently changes the individual's personality structure. Secondly, like E.C.T., it has the power to abort endogenous depressive moods, without basically altering the mechanisms which underlie such moods. It is not unreasonable, therefore, to assume that in some cases an increase in energy analogous to the increase in appetite often noticed after operation may through the activation of basic emotional drives and the arousal of normal interests provide a primary contribution to the alleviation of symptoms. The occasional

development of manic states after leucotomy, as after E.C.T., supports this thesis.

As with E.C.T., this power to abort depressive reactions is not absolute, and severe depressions may remain unaffected, or may be only transiently relieved. Unlike E.C.T. leucotomy also produces specific personality changes. It reduces the patient's tendency to anxious rumination and his power to sustain psychologically determined moods. Apart therefore from its value in some severe personality disorders leucotomy is particularly useful in those depressive states where an autonomous depression is maintained by anxiety or obsessional preoccupation. Of these some of the E.C.T.-resistant involutional depressions are the best example.

To sum up, therefore, the observations made at Queen Square support two hypotheses: Firstly, that some endogenous depressions are prognostically and ætiologically distinct from most reactive depressions and, secondly, that leucotomy exerts a specific but transient effect on the mechanisms underlying endogenous depression.

REFERENCES

ELITHORN, A., and BECK, E. (1955) *Lancet*, i, 23.
——, GLITHERO, E., and SLATER, E. (1958) *J. Neurol. Psychiat.*, **21**, 249.
——, and SLATER, E. (1956) *Brit. med. J.*, ii, 739.
GARMANY, G. (1958) *Brit. med. J.*, ii, 341.
PARTRIDGE, M. (1949) *J. ment. Sci.*, **95**, 795.
PIPPARD, J. (1956) *Brit. med. J.*, i, 1402.

Dr. Maurice Partridge (London) presented long-term results in 96 patients operated on by Mr. Wylie McKissock ten to twelve years previously, quite recently followed up again. 7 had died from unrelated causes. Of the 89 survivors, 46 had been continuously out of hospital for ten to twelve years. Incidence of epilepsy had risen to 15%. About one-third of the schizophrenic patients remained out of hospital. Recurrences of affective disorders had been milder. 7 obsessionals, previously totally incapacitated, had been able to lead an approximately normal life without relapse.

Mr. Wylie McKissock (London):

During the last twenty years I have stressed the experimental nature of leucotomy. I now believe, however, that leucotomy has passed from this stage of experiment to being an accepted practical form of treatment for certain forms of mental illness and I shall endeavour to prove this point.

After the establishment of the original Freeman-Watts technique of pre-frontal leucotomy the first modifications in technique were directed towards a more extensive section of the white matter in the pre-frontal regions. Examples of such modifications were those of Poppen and Lyerly in which, by using bone discs or bone flaps, the white matter could be divided extensively under direct vision. This type of operation arose as a result of the inadequate effect of the blind pre-frontal leucotomy upon serious and advanced cases of schizophrenia. Experience soon showed that, although the sting could more certainly be removed from the schizophrenic picture by these more extensive methods, the degree of undesirable personality loss increased with the area of cerebral cortex disconnected. The next phase of change in the technique of leucotomy was thus in the direction of diminishing the physical extent of the destructive lesion whilst endeavouring to place it accurately in certain strategic situations. In the course of this process arose the topectomies of Lawrence Pool, thalamotomy by stereotaxic coagulation designed by Spiegel and Wycis, Scoville's selective cortical undercutting of the prefrontal convolutions and of the orbital surface of the frontal lobes, cingulectomy, section of the fornix, &c.

Scoville's undercutting of the superior frontal convolution and my own rostral leucotomy were remarkably alike, although the lesion he made was the greater in extent. Rostral leucotomy was first performed by me in December 1948 and was then performed by open operation. The plane of section ran from a point a little in front of the coronal suture on each side, downwards and forwards to the frontal pole and measured some 1–2 cm. only in width. When the results of this small bilateral section proved inadequate the operation was converted into a blind procedure and produced rather more satisfactory results, the clinical effect appearing to be less extensive than that achieved by a standard pre-frontal leucotomy but more efficient than that of open rostral leucotomy.

The next modification consisted in directing the line of section farther backwards aiming at the junction of the middle and posterior thirds of the orbital plate. This leucotomy was labelled rostral G as the place of section seemed remarkably similar to that in which Grantham was making lesions by electro-coagulation. A series of patients subjected to the rostral G operation were reported upon by Pippard who suggested to me that the degree of personality loss or undesirable side-effect produced seemed to be

tending towards a degree of disability similar to that which followed a standard pre-frontal leucotomy. A further change in technique was therefore made, the line of section being placed somewhat farther forward than in rostral G, but farther back than in the original open and blind rostral procedures. The point of the brain needle in this type of operation is thus directed towards the mid-point of the orbital plate (Fig. 1).

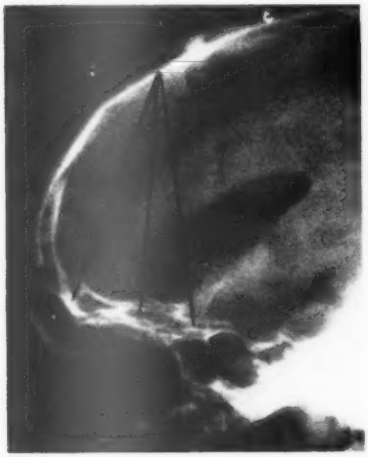


FIG. 1.

In honour of Dr. Pippard this operation is now designated rostral P and this has become my standard procedure in practically all cases with occasional exceptions.

In the very nearly twenty years that I have been practising leucotomy there has been a striking change in the type of clinical case referred for operation and it seems evident to me that psychiatrists have now a fairly clear concept of the type of symptomatology or syndrome likely to be beneficially affected by operation. This has been reflected in a marked diminution in the number of deteriorated schizophrenics offered for surgery although a number of dangerous or disturbed patients are still referred and can often be adequately sedated by a standard pre-frontal operation.

There has been a corresponding increase in the number of patients suffering from the symptoms of anxiety, tension, agitation and depression, who have failed to respond to all the other accepted forms of treatment. It is in this group as well as in the obsessional states that limited leucotomies seem to produce eminently satisfactory, even if not perfect results.

Rostral leucotomy was at first used rather sparingly but in more recent years has been performed far more frequently than has the standard operation. In 1957, for example, of 144 leucotomies personally performed, 125 were of the rostral P type and only 19 were standard Freeman-Watts procedures.

The mortality rate of rostral leucotomy is low in spite of the advanced age and poor general condition of many of the patients and in my own series of 490 such operations only 3 patients have died in the post-operative period. A further single patient died of bronchopneumonia eight weeks after operation and this death was possibly precipitated by the operation. If this is to be included there have still been 4 deaths in 490 cases, a mortality rate of less than 1%.

It is, of course, impossible for anyone but an observer studying a series of similar cases both before and after operation to decide upon the results of treatment or to contrast the variations between one form of operation and another, but I have seen nothing in the literature to convince me that thalamotomy, orbital undercutting or topectomy produces a higher percentage of satisfactory results than does rostral leucotomy.

Rostral leucotomy is a very simple procedure to an experienced neurosurgeon, requires no specialized apparatus or equipment and can be carried out in the simplest form of operating theatre. It can thus be performed in any mental hospital in the country without undue risk.

The 490 cases in my series have practically all, in fact, been operated upon in mental hospitals and not in fully equipped neurosurgical departments.

It is not an easy matter to obtain a large series of cases seen both before and after operation by the same psychiatrists although notable exceptions exist, as for example, the two series reported respectively by Partridge and Pippard, and Tennant.

It may, however, be considered permissible to examine the results of treatment in a single hospital where little change in the senior psychiatric staff has taken place and yet a considerable number of operations have been performed.

I chose Pen-y-Val Hospital, Abergavenny, as fulfilling these criteria and at this hospital have performed more than 170 leucotomies. At this point I should like to express my thanks to the Medical Superintendent, Dr. W. T. H. Wales, for all the trouble he has taken in recent months in providing me with full details of all the patients in the series and completing the follow up. 60 of these

patients have been subjected to rostral leucotomy.

Table I shows the gross results of all forms of leucotomy performed on 171 patients. Table II compares the results in all types of case treated by rostral and standard operations: 60% of the patients have left hospital and returned to full normal work, whilst 30%, although able to live out of hospital, are still not gainfully employed. 10% remain in hospital but live on a much happier level than they were able to pre-operatively.

The largest group in the series is that comprising the depressive illnesses and Table III shows the effect of rostral and standard leucotomy on such patients. In this group roughly two-thirds of the patients have left hospital and are at full normal work whilst the remaining one-third are still unable to work, though only 5% remain in hospital.

The psychotic and obsessional states form much smaller groups but are, none the less, worth examining in detail. Table IV gives the results of rostral leucotomy in the schizophrenic cases of which there were 17. Here only one-third are discharged and at work, the remaining two-

TABLE I.—GROSS RESULTS IN ALL CASES TREATED BY SOME FORM OF LEUCOTOMY
171 Patients

Discharged: Working	80	46·8%
Discharged: Not working	33	19·3%
Still in-patient	51	29·8%
Post-operative death	7	4·1%
Total	171	100·0%

TABLE II.—RESULTS OF TREATMENT

	Rostral leucotomy (60 cases)	Pre-frontal leucotomy (111 cases)
Discharged: Working	36 (60%)	44 (39·6%)
Discharged: Not working	18 (30%)	15 (13·5%)
Still in-patient	6 (10%)	45 (40·5%)
Deaths	—	7 (6·3%)
Total cases	60	111

TABLE III.—DEPRESSIVE STATES
Rostral Leucotomy—38 Cases

Pre-operative state	Post-operative state			
		Discharged: Working	Discharged: Not working	Still in-patient
Total incapacity in hospital	9	5	2	2
Total incapacity at home	8	4	4	0
Partial incapacity at home	21	16	5	0
Total cases	38	25 (65·8%)	11 (28·9%)	2 (5·3%)

Pre-frontal Leucotomy—60 Cases

	Total cases	Discharged: Working	Discharged: Not working	Still in-patient	Deaths
Permanent incapacity	32	10	4	13	5
Incapacitated at home	11	5	4	2	0
Partial incapacity at home	17	13	4	0	0
Total cases	60	28	12	15	5

TABLE IV.—PSYCHOTIC STATES
Rostral Leucotomy—17 Cases

Pre-operative state	Post-operative state			
	Total cases	Discharged: Working	Discharged: Not working	Still in-patient
Total incapacity in hospital	13	3	6	4 (all improved)
Total incapacity at home	0	0	0	
Partial incapacity at home	4	3	1	
Total cases	17	6	7	4

Pre-frontal Leucotomy—51 Cases

	Total cases	Discharged: Working	Discharged: Not working	Still in-patient	Deaths
Permanent incapacity	47	12	3	30	2
Incapacitated at home	1	1	0	0	0
Partial incapacity at home	3	3	0	0	0
Total cases	51	16	3	30	2

TABLE V.—OBSESSIVE COMPULSIVE STATES
Rostral Leucotomy—5 Cases

Pre-operative state	Post-operative state			
	Total cases	Discharged: Working	Discharged: Not working	Still in-patients
Total incapacity at home	3	3	0	0
Partial incapacity at home	2	2	0	0
Total cases	5	5	0	0

thirds being unemployed, or living at home or remaining as in-patients.

Only 5 patients suffering from obsessive-compulsive neurosis were operated upon but all have recovered to a point where they are leading normal lives and are working normally (Table V).

It seems to me quite clear that psychiatric knowledge has progressed to a stage where, when all conservative forms of treatment, including insulin therapy and E.C.T., have failed to produce a lasting result, it is now possible to choose with fair accuracy those who can benefit from rostral leucotomy. This is, I feel, a step forward and is due to the great attention which has been paid by psychiatrists to their patients before and after operation. Only by careful observation of the effects of surgery in relation to symptomatology could the present state of affairs, with a recovery rate of 60%, have come into being.

To sum up, rostral leucotomy has proved itself to be a form of treatment carrying a very low risk to life—less than 1%. It produces remarkably little undesirable side-effect and, when used in properly selected cases, chosen by experienced psychiatrists, offers a high rate of recovery.

Mr. G. C. Knight:

In 1949 Dr. R. Ström-Olsen and I decided to concentrate on division of the lower and inner fibres in the frontal lobe since we believed that "site" was of greater importance than volume in producing the good effect that is observed.

We adopted the operation of undercutting of the orbital cortex devised by Scoville but deliberately omitted the lateral portion of his incision to avoid damage in the outer part of the frontal lobe since undesirable changes have sometimes followed wounds in this region, and thus confined the incision to a narrow strip some 2 cm. wide passing down in the inner aspect of the lobe immediately above the orbital cortex to a distance of 5½ cm. This incision reaches a point immediately beneath the anterior limb of the internal capsule and is there in a position to sever that portion of the thalamo-frontal radiation that passes to the orbital cortex without disturbing other thalamo-frontal pathways going to the convexity and cingulate regions, and thus presumably leaves open a sufficient proportion of pathways to avoid undue flattening of emotion. We selected this approach since the results of animal experiment and the clinical observations of Rylander (1939, 1952) and others have shown that lesions in the orbital region in animals and man would produce tranquillity and loss of fear, a considerable potential benefit in agitated states.

This is an "open" operation which takes some two hours to perform, but we have been satisfied that it is well worth the greater effort since results have shown a notable absence of the undesirable side-effects sometimes seen in cases of "blind" leucotomy, such as excessive appetite and adiposity or intellectual or emotional blunting; indeed, these patients are warm and normal emotionally and many letters from relatives emphasize the entirely normal life and reaction of the patients after operation. In a few cases there has been a tendency to take things more quietly, which may represent a very slight degree of flattening, but the majority show no trace of this whatsoever.

Over 200 operations have been performed at Runwell Hospital and at the Regional Neurosurgical Centre at the Brook Hospital; all have been in patients in whom other forms of psychiatric treatment have failed, including psychotherapy, insulin, drugs, and E.C.T. In many cases the symptoms have been present for as long as five to twenty years. An interim review of the first 184 cases so far followed up is given in Tables I and II.

It is of interest that in 3 cases a second operation was performed where the first had failed and an extension of the incision of 1 cm. secured the desired effect. Likewise, the operation has succeeded when other forms of leucotomy have

TABLE I.—RESULTS OF TREATMENT CLASSIFIED ACCORDING TO DEGREE OF PRE-OPERATIVE DISABILITY

			Fully recovered	Improved No psychiatric treatment Slight symptoms	Failed	Deteriorated	Mortality	Epilepsy
C	*Psychiatrically disabled*, i.e. Out of hospital but in need of constant psychiatric help and treatment including drugs and E.C.T.	63	39	16	6	1	1 Hypertensive	3
B	*Socially disabled*, i.e. Out of hospital but unable to work	47	32	9	5	—	1 Hypertensive	2
A	*Totally disabled*, i.e. In mental hospitals ..	74	46	20	8	—		1
	Total	184	117	45	19	1	2	6

TABLE II.—RESULTS OF TREATMENT CLASSIFIED ACCORDING TO NATURE OF ILLNESS AND DEGREE OF PRE-OPERATIVE DISABILITY

		Schizophrenia	Agitated depression Anxiety neurosis Tension states	Depression	Obsessional	
117 Fully recovered	C	1	25 (1 case 2nd op.)	6	7	
	B	4	12 (1 case 2nd op.)	10 (One previous rostral)	6 (One previous rostral)	
	A	7	25 (1 case 2nd op.)	11	3	
		12	62	27	16	= 117
45 Improved	C	1	4	4	7	
	B	2	4	1	2	
	A	7	8	4	1	
		10	16	9	10	= 45
19 Failed	C	—	2 (early improvement)	2	2	
	B	2	1	2	—	
	A	4	2	1	1	
		6	5	5	3	= 19

failed and examination under direct vision has shown that the scar of the "blind" operation had failed to reach the point from which the good effect appears to be produced.

We believe that there is definite evidence that division of the fibres in the lower and inner part of the frontal lobe plays an essential part in producing the good effect which is observed in successful cases of leucotomy.

REFERENCES

RYLANDER, G. (1939) *Acta psychiat., Kbh.*, Suppl. 20, p. 3.

—— (1952) Premier Congrès Mondial de Psychiatrie, Paris, 1950. Paris; **4**, 356.

Meeting
December 4, 1958

MEETING AT THE NATIONAL HOSPITAL FOR NERVOUS DISEASES, LONDON

THE following cases were shown:

Weakness of the Proximal Limb Muscles from a Biochemical Cause (Hyperchloræmic Acidosis).—Dr. RAYMOND HIERONS.

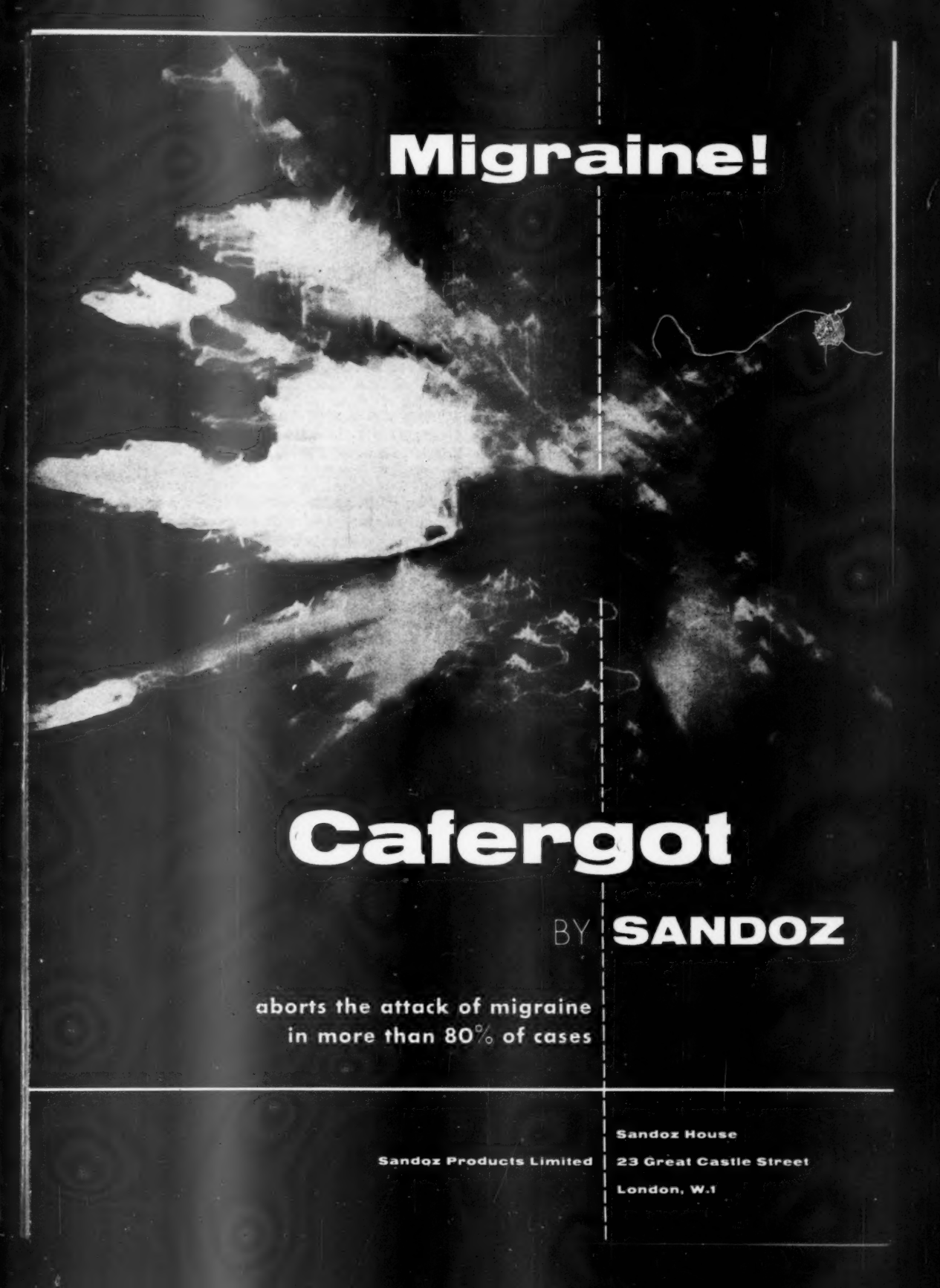
Facial Apraxia.—Dr. IAN MACKENZIE. (This case was also shown, by Dr. D. MCGILL, at a meeting of the Clinical Section held on December 12, 1958. A report of it will appear in the *Proceedings* in due course.)

An Unusual Example of the Parry-Romberg Syndrome.—Dr. P. KYNASTON THOMAS (for Dr. J. HAMILTON PATERSON).

Three Patients with Involuntary Movements Treated by Stereotactic Means: (1) Unilateral Tremor and Rigidity—18 years. (2) Bilateral Choreiform Movements—7 years. (3) Tremor and Stiffness of Left Upper Limb—16 years. —Mr. T. J. CONNELLEY (for Mr. HARVEY JACKSON).

Proximal Muscle Disease with Scleroderma—Dr. J. D. CARROLL (for Dr. DENIS WILLIAMS).

Association of Peripheral Neuropathy and Skin Lesions.—Dr. F. CLIFFORD ROSE (for Dr. MACDONALD CRITCHLEY).


Migraine!
Cafergot
BY SANDOZ
aborts the attack of migraine
in more than 80% of cases
Sandoz Products Limited
Sandoz House
23 Great Castle Street
London, W.1

Relief of
RHEUMATIC PAINS
with diethylamine salicylate

Algesal is the original skin-penetrating cream containing diethylamine salicylate. In 1955 a report of a clinical trial with Algesal appeared in the British Journal of Physical Medicine[1]. The report concluded:

"This preparation is a valuable addition to our therapeutic resources for the symptomatic relief of rheumatic pains. Clinical trial of 10% diethylamine salicylate cream *(Algesal)* showed significant relief of soft tissue rheumatic pains as compared with a dummy preparation."

Experimental work[2] has proved that diethylamine salicylate has a skin penetrative power 3 to 5 times that of other salicylates studied, and is completely non-irritating to the skin.

Over the past 5 years wide medical experience with Algesal has shown that symptomatic relief of common soft-tissue rheumatism can be achieved *without* counter-irritation, by the percutaneous route.

Algesal Balm contains the single active ingredient —10% diethylamine salicylate— in a soothing vanishing cream.

It is indicated in all the rheumatic syndromes seen in general practice: fibrositis, lumbago, osteo-arthritis, tenosynovitis, pain and stiffness after exercise.

Pads of tear-off leaflets describing special remedial exercises are available for giving to patients with lumbo-sacral strain, osteoarthritis of the knee, frozen shoulder and painful foot strain.

[1] March 1955. p.62
[2] Halpern, B., Gaudin, O., et al (1948) C. R. Soc. Biol. (Paris) **142**, 819

Algesal

percutaneous salicylate cream for the relief of rheumatic pain by injunction

Samples and full descriptive literature available on request to

E.G.H. LABS. Peru Street, Salford 3, Lancs.

Proceedings of the Royal Society of Medicine

Vol. 52
211

Section of Pathology

President—Professor R. J. V. PULVERTAFT
O.B.E., M.D., F.R.C.P.

Meeting
November 4, 1958

Renal Biopsy [*Abridged*]

By R. H. HEPTINSTALL, M.D., and A. M. JOEKES, M.R.C.P.
London

THE first accounts of percutaneous renal biopsy were those of Perez Ara (1950) and Iverson and Brun (1951), the latter describing their results of 80 biopsies. Since then numerous publications have appeared and biopsy of the kidney is now a well-established and safe procedure. We have had experience of 136 percutaneous biopsies out of a total of 142 attempts performed by the method described by Kark and Muehrcke (1954). The material is fixed in 10% formol saline and, after paraffin embedding, serial sections 5 μ thick are cut and mounted 6 per slide. Every fourth slide is stained with hæmatoxylin and eosin and appropriate slides are stained with hæmatoxylin and van Gieson's mixture, by the periodic acid-Schiff method and with methyl violet for amyloid. Other special stains are used when indicated. When necessary, additional material is removed and fixed in cold acetone for enzyme staining, or used for bacterial culture. The average number of glomeruli available for examination in our series was 23 with a range of 3–51. There were few complications; perinephric bleeding occurred in 2 patients, 1 of whom had to be transfused, and hæmaturia with colic, requiring pyelostomy, in 1.

The main indications are as follows:

(1) To make a firm histological diagnosis:

(*a*) To assess prognosis. (*b*) To compare the efficacy of different therapies in diseases whose nature can be determined only by biopsy; for example, to evaluate steroids in the treatment of the nephrotic syndrome. (*c*) To determine whether the lesion causing acute renal failure is reversible and decide whether efforts to prolong life with repeated hæmodialysis are justifiable. (*d*) To determine the status of the opposite kidney when nephrectomy is contemplated.

(2) Investigative procedures:

(*a*) To study the evolution of diseases of the kidney. (*b*) To study renal lesions in non-fatal conditions. (*c*) To study renal disease using newer techniques such as enzyme staining and electron microscopy.

(3) To obtain material for bacterial culture in the diagnosis and study of pyelonephritis.

The following are a few of the conditions we have studied in this series of biopsies:

Nephrotic syndrome.—34 cases of the nephrotic syndrome have been studied and an account of the first 20 of these has been published elsewhere (Joekes *et al.*, 1958). A wide variety of conditions was encountered, as follows: Ellis Type II nephritis 13, renal vein thrombosis 4, focal glomerulonephritis 7, mercury intoxication 2, acute diffuse glomerulonephritis 1, no recognizable abnormality 5. In addition one showed the changes of benign nephrosclerosis, and one only a few minor glomerular abnormalities. The chief importance of renal biopsy in this syndrome is that a rational assessment of steroid therapy can be made in the light of a precise histological diagnosis. The fallacy of claims of cure without knowledge of the underlying disease process is apparent.

Systemic lupus erythematosus.—6 cases have been studied, 2 by repeated biopsy. All had protein and abnormal cells in the urine. The most common abnormality, present in 4 of the cases, was an increase of cells in rounded areas at the periphery of individual tuft lobules with or without necrosis. Only some glomeruli showed these changes, the others being normal. "Wire loops" were found in only 2 cases, but in 1 of these the capillary basement membrane of the glomerular tufts was diffusely thickened. Intracapillary hyaline thrombi were found in the glomerular tufts in 2 cases. In no case were hæmatoxyphil bodies seen.

Schönlein-Henoch syndrome.—7 cases of this syndrome, in whom hæmaturia and proteinuria were present, have been biopsied. A normal histological picture was seen in 2, a focal glomerulonephritis was seen in 4, and 1 was normal except for a few scarred glomeruli. Up to the present time the only pathological picture recognized is the florid type of glomerulonephritis found in patients dying in uræmia and we have no knowledge of the renal lesion in the milder cases.

Acute diffuse glomerulonephritis.—4 patients.

with acute diffuse glomerulonephritis have been biopsied. A second biopsy was performed in 2 of these two and five months later. The lesion consists of an increase in nuclei, sometimes with a neutrophil increase in every glomerulus. One of the two repeat biopsies (five months later) showed an almost complete resolution. These cases are of great interest as the histological changes are similar to those found *post mortem* in the kidneys of persons dying from acute glomerulonephritis on which our knowledge of this disease is based. It was surprising that proliferative lesions were present so long (ten weeks in one case) after the onset of the illness.

These examples from the total number of cases studied show quite clearly the importance of renal biopsy. It is a procedure that will undoubtedly help to solve many of the outstanding problems of renal disease, but we feel most strongly that at the present time it should not be carried out in an unsystematic way and is likely to produce its best results only when there is close and continuous co-operation between clinician and pathologist.

REFERENCES

IVERSON, P., and BRUN, C. (1951) *Amer. J. Med.*, **11**, 324.

JOEKES, A. M., HEPTINSTALL, R. H., and PORTER, K. A. (1958) *Quart. J. Med.*, **27**, 495.

KARK, R. M., and MUEHRCKE, R. C. (1954) *Lancet*, i, 1047.

PEREZ ARA, A. (1950) *Bol. Liga Cáncer, Habana*, **25**, 121.

Some Aspects of Magnesium Metabolism and Magnesium Deficiency

By I. MACINTYRE, M.B.

London

ALTHOUGH magnesium is the fourth most abundant cation in the body (after calcium, sodium and potassium) we know relatively little of its main functions *in vivo* and even less of its importance in disease. An adult man contains about 2,000 mEq. of magnesium (25 grams) and on an average diet ingests about 25 mEq. every day. Of this amount about one-third is absorbed and excreted in the urine while two-thirds pass into the fæces.

Like potassium, magnesium is present inside the cell in much greater concentration than in the extracellular fluid. It was once believed that potassium was retained inside the cell by a relative impermeability of the cell membrane; this notion was finally dispelled only when Noonan *et al.* (1941) showed that injected radioactive potassium rapidly mixed with all the potassium in the body of a rat, whether inside or outside of the cell. A suitable isotope of magnesium to carry out similar experiments has not been available until recently, so that those static concepts of impermeability discarded for potassium have been retained for magnesium.

I shall first describe some experiments with radioactive magnesium, mention briefly magnesium and oxidative phosphorylation, and finally discuss experimental magnesium deficiency in the rat.

Experiments with radioactive magnesium.—^{28}Mg has a half-life of twenty-one hours and emits β and γ rays of sufficient energy to be recorded easily with standard equipment. Small quantities can be obtained "carrier-free".

An intraperitoneal injection of radioactive magnesium was made in five hooded rats weighing about 185 grams (171–202 grams). The rats were killed at intervals up to two days, and samples of the various tissues obtained. The total magnesium content and radioactivity were then measured in each sample. Flame spectrophotometry (MacIntyre and Davidsson, 1958) was used for determination of magnesium. Fig. 1 shows the specific activities of the various tissues plotted as a function of time. These figures are a measure of the extent to which the radioactive magnesium mixed with the stable magnesium in the tissues. Although these figures are uncorrected for the slightly differing weights of the animals, three features are striking:

(1) Most of the bone magnesium does not exchange rapidly. (2) At twenty-four hours the specific activity in muscle is less than half that of plasma. (3) The magnesium in the vital organs exchanges much more rapidly.

We may conclude that magnesium may exist in at least two forms in skeletal muscle, and that it readily crosses the cell membrane. It is clear that the high intracellular concentration of magnesium is maintained by something other than membrane impermeability, possibly by active transport.

Magnesium and oxidative phosphorylation.—In the body, the energy released by oxidation of foodstuffs is partly stored in high energy phosphate bonds. Mitochondria can be isolated from cells, and are able to carry out this process of oxidative phosphorylation, *in vitro* under suitable conditions, which usually include the presence of magnesium. High concentrations of thyroxine in the medium lower the proportion of phosphate

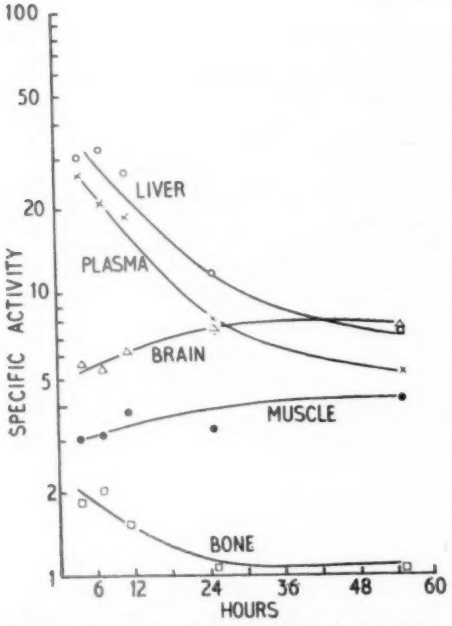


FIG. 1.—Tissue specific activities following intraperitoneal injection of ^{28}Mg in the rat.

bonds produced to oxygen consumed (Martius and Hess, 1955). In lower concentrations, thyroxine produces a damaging swelling of mitochondria, an effect opposed by magnesium (Tapley, 1956). Vitale *et al.* (1957) claimed that mitochondria isolated from rats after only a few days of magnesium depletion showed lowered P : O ratios, and it seemed that this might represent an *in vivo* counterpart of the laboratory effects described above. However, Beechey *et al.* (1959) failed to confirm these results, and if magnesium deficiency affects oxidative phosphorylation *in vivo*, it may do so only after prolonged deficiency or in a small proportion of cells.

Experimental magnesium deficiency. — The characteristic signs of magnesium deficiency in the rat were first described by Kruse *et al.* in 1932. Their description was amplified and confirmed by Watchorn and McCance (1937), by Tufts and Greenberg (1938) and by other later workers.

The progress of the deficiency is dramatic. Two stages are observed; after a few days intense peripheral vasodilatation occurs which then fades and leads to a stage of hyperexcitability, convulsions and weight loss.

MacIntyre and Davidsson (1958) repeated these studies with particular reference to the effects produced on the other electrolytes. Contrary to earlier reports, a progressive decline in the magnesium content of the skeletal muscle was observed. Further, although the diet contained ample potassium, a large loss of this ion occurred. This secondary potassium loss may be ascribed to a failure of energy production in muscle due to the loss of magnesium.

In agreement with previous workers, we found that nephrocalcinosis was produced; we were able to show, moreover, that this was accompanied by hypercalcæmia which eventually became extreme. In further experiments (Hess *et al.*, 1959) we were able to show that intracellular calcification occurred in the distal part of the proximal convoluted tubule. The intracellular calcium deposits later irrupted into the tubular lumina where they were seen as casts.

Identical lesions are produced in the same sequence in the same cells by vitamin-D intoxication (Scarpelli *et al.*, 1959), and by parathyroid hormone (Engfeldt *et al.*, 1958). In the latter case, renal concentrating power was markedly impaired, and recovered when parathyroid hormone was stopped.

Discussion.—These results suggested to us that this distal part of the proximal convoluted tubule may be the site of renal calcium transport, whether influenced by vitamin D or by parathyroid hormone. Further, these cells seem to be particularly sensitive to change in serum magnesium in such a way that diminution in serum magnesium produces an effect similar to overdosage with vitamin D or parathyroid hormone.

It may even be that this postulated effect of magnesium on calcium transport extends to the gut; Fitzgerald and Fourman (1956) found increased calcium absorption in healthy subjects on a magnesium-deficient diet.

Hazardous as it is to transfer results from one species to another, one cannot help speculating whether the locally indistinguishable granulomata of sarcoidosis and berylliosis result from similar local enzymatic lesions; beryllium will certainly inhibit magnesium-dependent enzymes and produce a relative magnesium deficiency. It is even possible that the hypercalciuria and hypercalcæmia of sarcoid and the hypercalciuria of berylliosis (Henneman *et al.*, 1956) are all systemic manifestations of the absorption from the granulomata of substances mimicking, like magnesium deficiency, the action of vitamin D.

Whatever the truth of these speculations, I should like to emphasize two main points in summary: (1) Magnesium in the vital organs is rapidly exchangeable, and cannot be regarded as existing as an inert stable compound. (2) A low serum magnesium, even if only transitory, may be disadvantageous to the kidney, and may be permanently damaging if prolonged.

REFERENCES

BEECHEY, B., *et al.* (1959) *Biochem. J.* In press.
ENGFELDT, B., GARDELL, S., HELLSTRÖM, J., IVEMARK, B., RHODIN, J., and STRANDH, J. (1958) *Acta endocr. Copenhagen*, **29,** 15.
FITZGERALD, M. G., and FOURMAN, P. (1956) *Clin. Sci.*, **15,** 635.
HENNEMAN, P. H., *et al.* (1956) *J. clin. Invest.*, **35,** 1229.
HESS, R., *et al.* (1959) *Brit. J. exp. Path.* In press.
KRUSE, H. D., *et al.* (1932) *J. biol. Chem.*, **96,** 519.
MACINTYRE, I., and DAVIDSSON, D. (1958) *Biochem. J.*, **70,** 456.
MARTIUS, C., and HESS, B. (1955) *Biochem. Z.*, **326,** 191.
NOONAN, T. R., FENN, W. O., and HAEGE, L. (1941) *Amer. J Physiol.*, **132,** 474.
SCARPELLI, D. G., TREMBLAY, G., and PEARSE, A. G. E. (1959) *Amer. J. Path.* In press.
TAPLEY, D. F. (1956) *J. biol. Chem.*, **222,** 325.
TUFTS, E. V., and GREENBERG, D. M. (1938) *J. biol. Chem.*, **122,** 693.
VITALE, J. I., NAKAMURA, M., and HEGSTED, D. M. (1957) *J. biol. Chem.*, **228,** 573.
WATCHORN, E., and MCCANCE, R. A. (1937) *Biochem. J.*, **31,** 1379.

DISCUSSION

Dr. S. C. Agarwal: Dr. MacIntyre has shown the marked contrast in the vasodilatation in the ears of normal and magnesium-deficient rats. I wonder if he could throw any light on the pathogenesis of vasodilatation in magnesium-deficient rats. It might be that magnesium deficiency is in some way related to the contractility of the smooth muscle cells in the terminal arterioles and capillaries. It seems likely that the effect of a deficit in magnesium ions is mediated through its action on A.T.P.-ase resulting in an unusual splitting of phosphate radical from adenosine triphosphate and an increased formation of adenosine diphosphate. The latter is a vasodilator and its increased accumulation will lead to vasodilatation.

Dr. MacIntyre, in reply: I would certainly agree with Dr. Agarwal that an increase in adenine nucleotides in the blood might well be the cause of the peripheral vasodilatation. This possibility had previously been suggested to me by Dr. Holton and we intend to investigate this in future work.

Epidemic Nephritis in North Yorkshire [*Abstract*]

By D. J. PAYNE, M.B., Dip. Bact.
Northallerton

IN March 1958, when we were in the middle of an epidemic of acute nephritis, I looked through the literature and found only one account reported from the United Kingdom. True epidemics were comparatively rare although there are many reports of minor outbreaks.

14.000 cases were reported to have occurred during the American Civil War and over 1,000 cases of trench nephritis were reported from the British Army in France and Flanders during the first year of World War I (Brown, 1916). Epidemics were common at the end of World War II (Formijne, 1948; Pratas, 1944; Cascalea *et al.*, 1945). Just after the war, 159 cases were admitted to hospital in Greenock and five times as many cases were estimated to have been treated at home (Fleming, 1949). In 1953, Rammelkamp and Weaver in America and, in the following year, Wilmers *et al.* (1954) in this country showed the association of nephritis with *Streptococcus pyogenes* type 12.

This is an account of an epidemic of acute nephritis in North Yorkshire. 5 cases occurred in a small village in 1957, during the first two months of the year. Throat and nasal swabs from the local schools showed that there was a high incidence of *Streptococcus pyogenes* type 12 infection in these schools. Urines of the children showed albumin, red cells, and casts in some cases, which, when compared with urines from children in schools 25 miles away, indicated kidney damage. In all, 38 children, 10 of whom had type 12 strains in their throats, had evidence of kidney damage. Sixteen months later, 7 out of 38 still have abnormal findings—5 with albumin, 1 with red cells and casts, and 1 with red cells only. No more cases occurred until December 1957. From then until November 1958 cases occurred in the Northallerton area and York mainly during the January–March period as before. 24 cases from the Northallerton area yielded 10 type 12 strains and, in York, 9 type 12 strains were isolated from 25 cases and type 22 from another. In all more than 60 cases of acute nephritis have occurred in the area. The ages ranged between 4½ and 50 years, 25% being over 21 years of age. The male to female ratio was 2 to 1. Only 4 out of 32 did not have a history of sore throat or otitis media. Mildness of the initial symptoms was a feature, as was a shorter latent period between infection and the onset of nephritis than has been described. Follow-up of the cases is proceeding and might, in time, throw light on the ætiology of chronic nephritis.

Since November 1958 the epidemic has spread northwards to Tees-side where at least 19 cases have occurred and the first death in the epidemic has been reported (Blowers, 1959).

REFERENCES

BLOWERS, R. (1959) Personal communication.
BROWN, L. (1916) *Brit. med. J.*, ii, 723.
CASCALEA, M. C., *et al.* (1945) *Medicina, B. Aires*, **6,** 21.
FLEMING, J. (1949) *Lancet*, i, 763.
FORMIJNE, P. (1948) *Acta med. scand.*, **129,** 509.
PRATAS, S. (1944) *Amat. lusit.*, **3,** 559.
RAMMELKAMP, C. H., JR., and WEAVER, R. S. (1953) *J. clin. Invest.*, **32,** 345.
WILMERS, M. J., *et al.* (1954) *Lancet*, ii, 17.

For further details *see Brit. med. J.*, 1958, ii, 1381.

Proceedings of the Royal Society of Medicine

Vol. 52
215

Section of Laryngology

President—R. L. FLETT, F.R.C.S.

Meeting
November 7, 1958

Pharyngitis

PRESIDENT'S ADDRESS

By R. L. FLETT, F.R.C.S.

Derby

IN this paper I am excluding infectious diseases, tuberculosis and syphilis. The last time large numbers of acute pharyngitis were seen was at the time of Wimbledon throat in 1938. There the first infectivity may have been a virus, but a streptococcus was the final invader, and a brick-red throat was seen with brawny œdema, and these people were fairly ill. The best description obtained from a patient was, "My throat feels set in cement". The worst type of acute pharyngitis was often known as hospital throat; this was usually a fulminating illness with surrounding cellulitis, and sometimes spread into the parapharyngeal space. Pharyngitis also sometimes followed injury by foreign bodies. All these now are readily dealt with by antibiotics. The modern concept of this condition is that it is important to differentiate between a virus pharyngitis and a streptococcal one. The virus is APC type 3; it is so called from the name adenoidal, pharyngo-conjunctival fever. The pharyngitis is that which is associated with the common cold, and is a mild self-limiting disease of three to five days. By means of numerous and complicated tests virus behaviour can be studied readily and prognosis laid down. The investigation in America began with the 1951 Greely, Colorado, outbreak, and has been continued by Cockburn *et al.* (1956). A separate investigation has been carried out by Dingle *et al.* (1955), and Bell *et al.* (1955).

Streptococcal pharyngitis is recognized as a possible cause of rheumatic fever, glomerulonephritis, and a carrier state. The important condition as far as the physicians are concerned is rheumatic fever. As might be expected, this seems to become more important when large numbers of human beings are collected together, for example in Army barracks, schools and universities. As regards rheumatic fever, a U.S. Army investigation (Catanzaro *et al.*, 1955) treated 500 cases with oxytetracycline, and kept 480 cases on treatment by antiseptics alone.

Their findings were that the treated cases had 5 cases of rheumatic fever, the controls 12 cases. The only disadvantage from treatment was that the treated cases had many more recurrences, usually two to three weeks later. From this liability there has sprung quite a large literature on the best method of treatment of acute streptococcal pharyngitis, first by one large injection only, or smaller ones once daily, or twice daily. Bischoff (1955) has drawn attention to the amount of acute infective sinusitis and tonsillo-pharyngitis prevalent in Western Texas, due to almost constant dust-laden winds. His treatment has been penicillin injections, and local use of a spray of bacitracin, neomycin, polymixin B, and a vasoconstrictor. In my opinion, the antibiotics are effective by injection, or by mouth, or by insertion into wounds, or raw cavities, but are ineffective on a mucous surface, and not as good as antiseptics, or even an alkaline wash. Indeed in sensitive individuals they have the power of denuding the mucosa of its surface cells, and this usually makes the inflammation continue for another two to three weeks. There is, however, one practical point brought out by Bender (1956): a case of infectious mononucleosis, which happened also to have acute streptococcal pharyngitis. This was masked by the glandular fever symptoms, and the patient later developed heart changes as shown by the electrocardiogram. The possible complications in glandular fever are numerous, but, in a large outbreak, this must be remembered.

Herpetic conditions in the pharynx.—In herpes simplex it is a curious fact that the lesion occurs, for example, on the face or lip in usually the same site time after time. This holds good for the pharynx and soft palate, and very often the bleb becomes a blood blister which bursts and causes great alarm. By the time the patient is seen, a shallow ulcer is present.

Herpes zoster.—It is well known that geniculate herpes may occur on the anterior pillar of the fauces. Involvement of the vagus nodosal ganglion can cause paralysis of the constrictors, difficulty in swallowing, analgesia, and also vesicles which may occur on the epiglottis and arytenoids with paralysis of one vocal cord.

Chronic pharyngitis may be said to include a large variety of conditions which may extend from anatomical variations to a neurotic ætiology, as well as a number of chronic ulcerative conditions again not specific in character. At a discussion on this subject opened by Bedford Russell (1931) the consensus of opinion condemned the nasal sinuses. The treatment has been irrigation of the antra, especially when an X-ray investigation revealed dullness of the sinuses. Most often this resulted in obtaining only a few shreds of mucus, which meant probably slightly thickened mucous membrane, and no improvement was noticed in the condition of the pharynx.

When very severe infection is present in the nose and nasal sinuses, with production of large amounts of thick pus, the patient seldom complains of symptoms of pharyngitis. The postnasal discharge produces large thickened lateral pharyngeal columns continuing up into the nasopharynx like lateral adenoids, and the symptoms are those of nasal obstruction, and discharge, and no complaints referable to the pharynx.

Sinus infection, as far as chronic pharyngitis is concerned, is now not really what it was. The infective environment in civilization is many times reduced in virulence, and it is only seldom that an antral lavage produces thick creamy pus. We are therefore inclined to turn to the diatheses. The patient complaining of his throat is more likely to have slight lateral pharyngeal columns, with varying redness. There is nothing to be seen in the nose, and mild changes in the nasal sinuses, yet he complains bitterly about his throat symptoms.

Allergic conditions in the nose and sinuses are the most common cause, and the changes seen in the nose can vary from the most severe swelling of the whole nasal mucosa to slight changes on the anterior ends of the middle turbinates. This latter type of patient is the one most liable to chronic pharyngitis, and the symptoms settle readily with antihistamines and encouragement. It is important for the patients to be told that there are only slight changes in the throat; if they express any doubt, I then say that any further investigation of this complaint is likely to be more troublesome than their symptoms. The antihistamines, I consider, have the power of reducing the thickening of the mucous membrane, and so increasing the calibre of an ostium of a nasal sinus. Any superadded infection will then be cleared out more efficiently by the cilia. It is necessary to change the antihistamine frequently to find out which drug will suit each patient, and also to avoid undesirable side-effects.

Patients were commonly sent to bacteriologists, and used to hand in, with more pride than concern, a long list of the bacteria that had been discovered in their throats. Except for the streptococcus, bacteria have been treated with contempt and neglect as usually they are non-pathogenic. The long list has only ensured that the efforts at encouragement, reassurance and debunking should be asserted with some salesmanship. Recently the staphylococcus with its development of resistance to antibiotics has become much more important.

The plethoric diathesis readily causes the development of chronic pharyngitis, especially if it is combined with a high blood pressure. A patient with an angry-looking face and bull neck usually possesses a pharynx which looks angry. He perhaps is a foreman in a foundry, works in a hot dry atmosphere, and has to do a great deal of shouting over the noise in the foundry. He has a rasp in his voice, and it is important to try to reduce his weight, and cut down his shouting.

Alcohol can be a most important cause of pharyngitis—not beer, but spirits—and especially when they reach a bottle a day. Alcoholic laryngitis, in my experience, usually means death in about six months from delirium tremens. People with pharyngitis, however, seem to have more resistance, and better livers, and seem to last a great deal longer. Unfortunately, they readily develop carcinoma *in situ*. I have recently seen such a patient who had a carcinoma in the fauces, and nine months later a subglottic carcinoma; apparently two primaries. An alcoholic seems to show much less resistance to the spread of carcinoma and, when treated, more readily develops a recurrence.

Another type of patient is one with a congested throat and no apparent cause, very often a man in his twenties: there may even be dilated capillaries up to small telangiectases in the throat like that in rheumatoid with amyloid disease. Very often this is due to severe dental caries or gum infection. In this case, a prickling or tickling sensation is the complaint. There may be some dyspepsia, and perhaps constipation.

Another patient is the aggressive little woman with pain in the throat and neck on one side with nothing to see on examination. After a few minutes she gives the impression that it is my fault she has these complaints. Then a protective mechanism is called into play, to prevent the full weight of medical and surgical investigation falling upon her. It is found that she is rapidly running through all the medical practitioners in the district, as at the end of every three months she is told to take her card to

some other doctor. I try to reason with her, and if I am unsuccessful, then she is sent to the psychiatrist. This may also be the end-result of some of our acute conditions, which have developed chronic symptoms without any pathological change locally.

Very often there is a feeling of fullness in the throat, and this is most frequently a sequel to a death in the family. Perhaps it is the result of sorrow, that is, the well-known lump in the throat, or it may be the sudden cessation of hard work and great anxiety. This condition is very common in people who have been nursing patients dying of carcinoma of the larynx or pharynx. It is said to be due to spasm of the cricopharyngeus, and assurance that there is nothing significant in the throat usually causes the patient to agree with that point of view.

Chronic pharyngitis is a much more common complaint in public speakers than laryngitis. Huskiness is less common in these people than an ineffective voice, tired throat muscles, dryness and inability to make the voice carry. It seems to deprive their voice not so much of conviction but sincerity, and assumed sincerity is most important to a salesman. I enjoy explaining to an alderman that he has clergyman's sore throat. Usually this starts with a minor acute pharyngitis, possibly after a cold, and their attention subsequently is centred on their most important gift, the voice. It may be that he speaks in two tones, or that he is frightened that the voice may entirely give out, or whisper, or give him cramp. Assurance is required, perhaps, if the patient is young, correction of voice production, and sometimes an oily nasal spray.

For local treatment sprays or lozenges can be used, whenever the patient seems to look for treatment. Especially is this so in the patient bedridden from rheumatoid arthritis, secondary carcinomata in the spine, or hemiplegia. For the others exercise is more important.

In children the most important symptom is the hard dry cough. In adults this symptom seems now to be less common. With some patients, I used to associate it with drinking of port in large amounts. In allergic people port and sweet liqueurs can bring on slight bronchospasm, and a lot of these folk seem to know that alcohol of this type does not suit them. Some patients complain of cough in a sudden drop in temperature; I had one patient who had chronic pharyngitis, and who used to tell me that he would wake up with his cough at 3 a.m., and on looking at his bedside thermometer, found that it was 63° F. instead of 65°. Whenever I had asthmatic attacks, I used to notice that there seemed to be too much saliva, and a swallow seemed unable to clear just above the larynx. This tended to start a hard cough, which sometimes might bring on the difficulty with expiration. Repeated swallowing became necessary, even although I told myself I must not become neurotic. This is the same repeated swallowing that can occur with sea-sickness, although the saliva then seems to be much more abundant. Dry digestive biscuits are a great help.

In children the hard dry cough goes on all night, but it is more distressing to the worrying parents than to the child, who manages to sleep through it all. It is not so much due to lateral pharyngeal columns, as to nodules or granulations on the posterior wall, and these often are attempts to replace lymphoid tissue which has disappeared in the too early removal of tonsils and adenoids. The nasopharynx which is too large as a result of scarring of the fauces is, I consider, due to dissection of the tonsils, and too enthusiastic removal of the triangular area between tonsil and lingual tonsil. Sometimes the lingual tonsil is scarred up into the tonsillar fossa, and in others the soft palate is dragged down laterally, so that its posterior margin is lower and more anterior. This results in a large dry nasopharynx, and with each cold a dry diffuse inflammation occurs, readily leading to acute otitis media. Another post-operative possibility is the ablation of the ridge of Passavant, in removing adenoids with a curette with the head extended instead of flexed, and too much follow-through. This is one reason why I have continued to use the adenotome.

The too long styloid process with inflamed overlying tonsil may cause pain in the ears. This used to be shortened at times, but I leave it alone, as the styloglossus is bound to lose its proper anatomical origin, and there is enough muscular inco-ordination and paræsthesia round the junction of the tongue and fauces without adding to it.

As to the uvula, I have shortened three, as far as I can remember, and have in each case required a good deal of *vis a tergo* from both practitioner and patient. It worked well in all 3 cases. In contrast, Sir James Dundas-Grant (1932) had 11 cases in two years. This of course was always for an irritating cough.

Another type of alteration in the pharyngeal mechanism is the difficulty in swallowing caused by spurs on the cervical spine, especially just above the larynx. They are due to cervical osteoarthritis, and have been removed after exposing the anterior surface of the vertebral column, by a mastoid gouge and hammer. The swallow was much improved.

Spondylitis again can cause pharyngeal

difficulties, when the cervical spine becomes fixed in lordosis.

Atrophic pharyngitis is due to the condition starting in the nasopharynx and not in the nose. Vallecular dysphagia most often accompanies an atrophic pharyngitis. The nasal mucous membrane is in a state of rhinitis sicca, but there are no crusts in the nose. The crusting starts in the nasopharynx and continues down the posterior pharyngeal wall. Tornwaldt's disease I have seen once. The crusting in the pharynx gives rise to a dry feeling but the patients do not complain much about the pharynx. The only symptom is huskiness as the crusts are also situated in the interarytenoid area in the larynx. I have seen this condition only in small anæmic women, and it seems to be founded pathologically on a sclerosing periarteritis and there has not been found any concomitant sinusitis. In Italy apparently it is noticed in 28% of workers in the textile industries (Carrara, 1957).

Sjögren's disease.—The mucous membrane of the tongue, palate and pharynx is so dry that to open the throat with a spatula is almost like tearing the mucous membrane apart. There seems to be a general atrophy of mucous, salivary, and lacrimal glands, and owing to the prolonged use of oily drops, some observers state that the patients are liable to die of lipoid pneumonia. Certainly I have been tempted for a short time to use liquid paraffin, and combined it with another lubricant, mica ground to about 15μ. However, I was saved from further disaster by a case of silicosis started in the mica factory, and therefore was able early to stop this treatment.

The pathology is said to resemble certain non-inflammatory lesions in the thyroid gland, in early stages Hashimoto's disease, and in the late stages myxœdema. Two-thirds of the patients already have rheumatoid arthritis, and some are later going to develop it.

It is very like a late result of Mikulicz's disease and some of my patients have had a swelling of the parotid gland. There can also be atrophy of the sweat glands. At the moment no local treatment seems to be of any use, and cortisone or its derivatives seem to be the only help.

The *Stevens-Johnson syndrome* is recurrent ulcers in the pharynx, mouth and lips, sometimes put down to *Streptococcus viridans*. One of my patients has had it for forty years, and has seen various consultants all over the country. His longest period of freedom from his ulcers has been four years; I had then put him on a vaccine from *Strep. viridans*, which had been found in an ulcer. His next recurrence, four years later, continued for about his usual three months, and did not react to treatment.

Behcet's disease (some of its symptoms are known as Reiter's disease or Rendu's) is a much more extensive phenomenon. It can affect the vulva or glans penis, the mouth and throat, also cause hypopyon, arthritis, and neurological changes which can lead to mental disease.

Post-cricoid stenosis is thought to be caused by a previous ulcerative state due to hypochromic anæmia. This can be dilated, and, if the anæmia is corrected, and the stenosis does not return, then the possibility of a neoplasm does not arise. If, however, the stenosis recurs after the second or third dilatation, a post-cricoid carcinoma is possible.

REFERENCES

BELL, J. A., ROWE, W. P., ENGLER, J. I., PARROTT, R. H., and HUEBNER, R. J. (1955) *J. Amer. med. Ass.*, **157,** 1083.

BENDER, C. E. (1956) *J. Amer. med. Ass.*, **161,** 13.

BISCHOFF, H. W. (1955) *Antibiotic Med.*, **1,** 285.

CARRARA, C. (1957) *Osped. maggiore*, **45,** 210.

CATANZARO, F. J., *et al.* (1955) *Ann. intern. Med.*, **42,** 345.

COCKBURN, T. A., ROWE, W. P., and HUEBNER, R. J. (1956) *Amer. J. Hyg.*, **63,** 250.

DINGLE, J. H., GINSBERG, H. S., GOLD, E., JORDAN, W. S., KATZ, S., and BADGER, G. F. (1955) *Trans. Ass. Amer. Phycns*, **68,** 73.

DUNDAS-GRANT, J. (1932) *Brit. med. J.*, i, 375.

RUSSELL, H. G. B. (1931) *Brit. med. J.*, ii, 485.

DISCUSSION

Mr. C. Gill-Carey said that pharyngeal ulceration of unknown origin could be divided into two clinical groups, two very simple groups: those who are likely to survive and those who must inevitably die. Friedmann reported that there had been some evidence that minor differences in the histological picture could be of prognostic importance.

In the first group he would place those cases of ulceration which were generally superficial, but occasionally deep enough to leave scarring. These ulcers, often multiple, were to be found in the mouth, nasopharynx and larynx, as well as the pharynx. After causing misery for years they would often, for no clear reason, disappear for ever.

In the second group, those associated with danger to life, could be placed the ulcers of malignant granuloma and of certain reticuloses. Amongst the latter would be found some cases in which no clue w s given by examination of the pharyngeal ulcer, the diagnosis being established by post-mortem.

Friedmann's recent records of 27 cases of malignant granuloma of the nose, upper respiratory and upper digestive systems, showed the value of histological differentiation between the localized and systemic forms of the disease. In the localized form 7 patients were well after radiotherapy, 1 for ten years, 2 for seven years, 3 for two to four years, and 1 for one year.

BIBLIOGRAPHY

FARMER, E. D. (1956) *Proc. R. Soc. Med.*, **49,** 640.

FRIEDMANN, I. (1955) *J. Laryng.*, **69,** 315.

HARRISON, K. (1952) *Proc. R. Soc. Med.*, **45,** 828.

BOOK REVIEWS

Brain—Memory—Learning. A Neurologist's View. By W. Ritchie Russell, C.B.E., M.D.(Edin.), D.Sc.(Oxon.), F.R.C.P. (Edin. and Lond.). (Pp. xii + 140; illustrated. 18s.) Oxford: Clarendon Press. 1959.

For the clinical neurologist, the chief interest and importance of Dr. Ritchie Russell's book will be his account of the physiology and pathology of concussion, his study of the traumatic amnesias and of traumatic epilepsy. His title does not reveal this significant component of his book, but deals with its more speculative aspect, namely, the consideration in terms of physiology of the processes of learning and memory, and the bases of character.

Some clear clues as to the possible physiological foundation of the two former are to be found in the classic papers of Sherrington and his collaborators, Graham Brown and Leyton, published in the early years of the century, and we may well doubt if any more significant observations have been made since. What has changed is simply the language in which these matters are discussed, and this is now the language of electronic recording methods.

Sherrington, however, was content to place on record his pregnant observations of the "lability" of the cerebral cortex—an unfortunate term under which much of the import of his discoveries has remained hidden—and he did not seek to leap the unbridged gap between physiology and psychology by proposing that the behaviour of the cortex could, by a suitable variation of vocabulary, be erected into an account of thought, memory, learning and so on. This, indeed, seems to be what is now being attempted. But to write of facilitation, cerebral alertness, synaptic knobs, nerve networks and reverberating circuits does not provide an account of thought, learning or memory, save for those who regard mental activities as no more than a sort of universe of nerve impulses in action. Of these, Jackson wrote that by solidifying the mind into a brain, they propose an easy settlement of a difficult problem.

Your reviewer believes that the present state of knowledge does not allow meaningful accounts of these mental activities in strictly physiological terms, nor does he believe with Dr. Ritchie Russell that the traditional distinctions between brain and mind, psychology and physiology are disappearing. They are in the nature of things and cannot be talked away.

Yet, the author makes a gallant attempt to correlate these two categories, and he will command the reader's respect for his courage in this, as he will achieve the reader's admiration for the clinically based chapters of his monograph. These reveal a wide and ripe experience.

Pneumoencephalography. By E. Graeme Robertson, M.D.(Melb.), F.R.C.P., F.R.A.C.P. (Pp. xxi + 482; illustrated. £5 10s.) Oxford: Blackwell Scientific Publications 1957.

This is by far the most important monograph we are aware of, dealing with the whole question of air-study of the brain. The author is a clinical practising neurologist of experience and distinction who, after his training in London, returned to Melbourne to take up an appointment as head of a department of neurology. To some extent he was perhaps a little isolated and the fairly novel technique of pneumoencephalography fell to his lot. With his customary care and thoroughness—even meticulous in its nature—Graeme Robertson set about learning and then perfecting his skill. It is doubtful whether, in any neurological or neurosurgical centre anywhere in the world, air-studies are carried out with greater success. Without undue resort to the literature of the subject, Graeme Robertson proceeded over the years to record his experiences, especially with reference to the technical finesses, his results and their correlation with brain pathology. The result is this present monograph, with its beautiful illustrations—comprising radiographs, photographs and the author's own line-drawings—which we believe is unique. Graeme Robertson's monograph is essential to the library of every neurologist, neurosurgeon and neuroradiologist.

Basic Surgery. Edited by Leslie Oliver, M.B., B.S.(Lond.), F.R.C.S.(Eng.), F.A.C.S. (Pp. xvi + 1360; illustrated. £6 6s.) London: H. K. Lewis & Co. Ltd. 1958.

The short preface states that: "This book has been written primarily for undergraduate students. . . . Sufficient operative surgery has been included to meet the needs of those students intending to specialize in surgery." The last phrase is ambiguous, but if it means "house surgeons and Fellowship candidates" the title and the preface raise the two fundamental questions: What is the basic surgery that an undergraduate student should know, and should one

attempt to cater for both undergraduates and postgraduates in the same textbook?

The policy of including operative details has not been consistently applied, otherwise the book would have been longer even than its present 1,360 pages. Operative surgery is given most space in the thoracic section, in which the chapter on pulmonary resection occupies 18 pages of operative and post-operative detail. In places, subjects other than operation are also discussed in greater detail than would seem indicated in an undergraduate textbook, for example the extremely detailed classification of the causes of hydrocephalus. For these reasons, we would regard this work as better suited to the Fellowship candidate, for whom it will be a good one-volume textbook, rather than to the undergraduate.

Though the term "basic surgery" is not defined, the 10-page chapter on Reactions to Injury by Dr. A. A. G. Lewis in the penultimate section of the book shows that brevity can be combined with profundity. If undergraduate students are to have time to consult monographs and original articles, as they should if medicine is to be regarded as a university subject, textbooks will have to be shortened. Perhaps the day will come when surgery for undergraduates will be dealt with in a real Textbook of Medicine written in co-operation by physicians and surgeons.

Milestones in Modern Surgery. By Alfred Hurwitz, M.D., and George A. Degensheim, M.D. (Pp. xvii + 520; illustrated. £5 12s. 6d.) London, etc.: Cassell & Co. Ltd. 1958.

This is an interesting collection of articles which have been milestones in the history of surgery. It starts with an account from Ambroïse Paré in which he described the dressing of wounds, and ends with descriptions of Gibbon's heart-lung machine and the homotransplantation of human kidneys between identical twins. Here will be found Sir Alexander Fleming's first note on penicillin, Torek's account of œsophagectomy in 1913 and Evarts Graham's description of the successful removal of a lung for carcinoma of the bronchus in 1933. Dr. Dunphy of Boston not only provides the foreword, but also one of the milestones.

This is the ideal book to put in the hands of a house surgeon since he will not only find it intensely interesting, but it will stimulate him to think about the way in which advances have evolved in the field of surgery.

> "Lives of great men all remind us
> We can make our lives sublime,
> And, departing leave behind us
> Footprints on the sands of time."

Operative Surgery. Edited by Charles Rob, M.C., M.Chir., F.R.C.S., and Rodney Smith, M.S., F.R.C.S. Progress Volume 1958 (pp. xiii + 100; illustrated); General Index (pp. 9 + 76). 60s. London: Butterworth & Co. (Publishers) Ltd. 1958.

An index volume does not normally call for review. The present volume contains, however, in addition to the index the announcement from the publishers: "To keep abreast of current practice 'Operative Surgery' will continue to be published in the form of progress volumes and to avoid a break in continuity the first of these books has been incorporated here." There are ten articles on a variety of subjects, the longest containing new observations on the surgery of the pancreas. Among other articles those on right hepatic lobectomy, aortic valvotomy, and femoro-popliteal arterial by-pass may be noted.

Textbook of Physiology and Biochemistry. By George H. Bell, B.Sc., M.D.(Glasg.), F.R.F.P.S.G., F.R.S.E., J. Norman Davidson, M.D., D.Sc.(Edin.), F.R.F.P.S.G., F.R.I.C., F.R.S.E., and Harold Scarborough, M.B., Ph.D.(Edin.), F.R.C.P.E., M.R.C.P. 4th ed. (Pp. xi + 1065; illustrated. 63s.) Edinburgh and London: E. & S. Livingstone Ltd. 1959.

The appearance of a new edition of Bell, Davidson and Scarborough has become a triennial event. The fourth edition has appeared promptly at the beginning of the ninth year since its inception. By judicious alterations in set-up, diagrams and plates and, where necessary, wording, the authors have managed to bring this volume up to date and at the same time to shorten it slightly. There is scarcely a section which does not show signs of revision either in text or diagram or both. The references at the ends of the chapters have been extended in line with the most recent work. The text and format are of the same high standard as in previous editions. The reputation it has earned as a students' textbook and a useful exposé of physiology in all its branches will be maintained and enhanced by this new edition and its price still remains reasonable.

Sensitivity Reactions to Drugs. A Symposium organized by the Council for International Organizations of Medical Sciences. Edited by M. L. Rosenheim and R. Moulton. (Pp. x + 237; illustrated. 35s.) Oxford: Blackwell Scientific Publications. 1958.

Symposia may either interest the specialist alone or else a wider circle. The present symposium interests both. Sensitivity reactions to

New publications from Pergamon Press . . . .

INTERNATIONAL SERIES OF MONOGRAPHS IN ORGANIC CHEMISTRY

SYNTHETIC ANALGESICS Vol. 1. DIPHENYL PROPYLAMINES

By **DR. PAUL A. J. JANSSEN,** *Beerse, Belgium.*

This book describes and discusses the present state of knowledge of the methods of synthesis, the physical and chemical properties as well as the analgesic activity of diphenyl propylamines. Other pharmacological properties of these compounds are also mentioned. The data are derived in part from many unpublished experiments conducted by Dr. Janssen's research group. The reliability of the data is discussed in detail. So far as possible the facts are presented in the form of tables, and theoretical considerations which cannot be translated into experimental terms are carefully avoided.

Price 45s. net [$7.50]

PSYCHOLOGICAL ANALGESIA IN OBSTETRICS

Journee d'Etudes sur les Methodes Psychologiques en Analgesie Obstetricale.

A SYMPOSIUM ORGANISED BY THE FRENCH SOCIETY OF PSYCHOSOMATIC MEDICINE HELD IN PARIS.

Edited by **P. ABOULKER, L. CHERTOK** *and* **M. SAPIR.**

In this book, a group of specialists from France, Belgium, Italy, Spain, Portugal, Switzerland and the U.S.A., discuss both the theory and application of painless childbirth, and, for the first time inside one cover, the claims of the different methods are considered—psychiatry, neurology, psychoanalysis, psychology, obstetrics. The medical psychological and social implications of painless childbirth by psychological analgesia are an important new feature of this book, and never before have the psycho-physiological aspects been discussed so fully.

Price £3 net [$10]

PSYCHOSOMATIC METHODS IN PAINLESS CHILDBIRTH

By **L. CHERTOK, M.B.**

Translated from the French by Denis Leigh.

The introduction of non-pharmacological methods of obstetrical analgesia has brought about a humanisation and a dedramatisation of the act of childbirth. Doctors, midwives and nurses have become more interested in the pregnant woman.

PSYCHOSOMATIC METHODS IN PAINLESS CHILDBIRTH describes the various non-pharmacological methods of producing analgesia—Read's method known as "childbirth without fear," the Russian method known as "psychoprophylactic preparation of pregnant women for childbirth"—and discusses their theoretical bases, separating the scientific from what still remains hypothetical. Dr. Chertok's study disposes of certain errors which are prejudicial to the methods and enables practitioners to act in a more rational manner.

Price 35s. net [$5.50]

QUANTITATIVE METHODS IN HUMAN PHARMACOLOGY AND THERAPEUTICS

PROCEEDINGS OF A SYMPOSIUM HELD IN LONDON, 1958

Edited by **D. R. LAWRENCE, M.D.,** *University College, London.*

Opening remarks by **SIR CHARLES HARINGTON, F.R.S.**

The 21 papers in this book bring together techniques for making measurements and for evaluating their accuracy, and give many examples of the invasion of pharmacology and therapeutics by mathematics and statistics. The emphasis is on the application of discoveries in pharmacology to the treatment of human beings, with particular attention given in the last section to the general considerations affecting clinical trials.

Price 45s. net [$7.50]

A LABORATORY MANUAL OF CHEMICAL PATHOLOGY

Edited by **Prof. R. T. G. PRUNTY, Dr. R. R. McSWINEY** *and* **Dr. JOYCE HAWKINS.**

The Laboratory Manual of Chemical Pathology will be welcomed by all technicians and other workers in this field who will want a personal copy for constant use. With its help, a competent worker should be able to cope with all the foreseeable demands of clinical chemistry.

The Manual is completely modern in its outlook and out-of-date methods are excluded, whilst some methods are included which are not yet in general use, but for which there will be increasing applications.

The book contains sections on basic manipulations and apparatus for the beginner and advanced sections showing the application of analyses to clearance determinations, body fluid measurement, and metabolic balance work. A unique presentation of the methods ensures complete absence of ambiguity and a thorough understanding of basic principles, so that the possibility of error is reduced to a minimum.

Price 30s. net [$5]

HÆMORRHAGIC NEPHROSO-NEPHRITIS

A. A. SMORODINTSEV, V. G. CHUDAKOV *and* A. V. CHURILOV.

Translated from the Russian by Catherine Matthews, M.Sc.

Among the infectious diseases little known to medical science, a prominent place is occupied by the group of viral hæmorrhagic fevers which are transmitted to man by blood-sucking ticks.

The present monograph is devoted to modern data concerning the ætiology, epidemiology, clinical features and pathological anatomy of hæmorrhagic nephroso-nephritis, by three authors whose systematic investigations have made them recognized authorities on the disease.

Price 60s. net [$9]

Fully descriptive leaflets on request

PERGAMON PRESS *London · New York · Paris · Los Angeles*

4 & 5 Fitzroy Square, London, W.1.

122 East 55th Street, New York 22, N.Y. 24 Rue des Ecoles, Paris V^e^

drugs are part of the cost of our increased therapeutic capabilities and are a challenge to both the research worker and the clinician. All aspects of the problem are covered, chemical, clinical, pathological, immunological and classificatory. A very useful feature is the consideration given to the value or otherwise of routine clinico-pathological investigation in the detection of sensitivity reactions. The varying reactions found lead into an intriguing no-man's-land where more questions are raised than have yet been answered. Nevertheless certain reaction patterns are becoming visible which can assist the clinician. The provision of a suitable index to the papers in the symposium makes the use of the whole volume much easier, and further, despite the differing nationalities of the contributors, all the articles are in English. The book is an excellent summary of the present knowledge and trends in this subject. It will become essential for reference as the results of studies in this field can be published in very different journals.

An Atlas of Esophageal Motility in Health and Disease. By Charles F. Code, M.D., Ph.D., Brian Creamer, M.D., M.R.C.P., Jerry F. Schlegel, B.S., Arthur M. Olsen, M.D., M.S., F. Edmund Donoghue, M.D., M.S., and Howard A. Anderson, M.D., M.S. (Pp. ix + 134; illustrated. 63s.) Springfield, Ill.: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1958.

The recent development of methods for measuring intraluminal pressures has made it possible to analyse the dynamics of deglutition. Much of the pioneer work has been done at the Mayo Clinic by Code and his co-workers who have designed manometric techniques for recording the complex sequences of pressure changes which occur on swallowing and for demonstrating the sphincteric mechanisms at the cardia and in the pharyngo-œsophageal region.

By applying these techniques to some disorders of œsophageal motility they have been able to clarify the nature of the lesions by analysing the disturbance of normal physiology in each disease. They have studied 100 cases of achalasia, several patients with diffuse spasm of the œsophagus and many cases of scleroderma. In this book they present their methods and results in pictorial form because the pressure recordings are largely self-explanatory. This method of presentation is very successful and the tracings have been well chosen and beautifully reproduced. The written word has been reduced to a minimum and no attempt has been made to review the literature or to supply a comprehensive bibliography.

Radioisotope Techniques in Clinical Research and Diagnosis. By N. Veall, B.Sc., F.Inst.P., and H. Vetter, M.D. (Pp. xii + 417; illustrated. 50s.) London: Butterworth & Co. (Publishers) Ltd. 1958.

Isotopes have come to stay, not only as tools of research, but in the everyday diagnostic armamentarium of many departments of our hospitals. Thus many doctors now find themselves forced to become amateur physicists if only to understand the techniques which they wish to employ.

This is undoubtedly the best book which has appeared on the subject, for it combines a wealth of sound information, simply presented, in a compact form and at a price which is half that of many similar publications. Veall is well known for his work in developing new techniques in the radioisotope field and Vetter from Vienna is likewise familiar to many people working in this country. Not only have they produced an eminently readable book, but it is beautifully printed on good paper, while the references at the end of each chapter give the titles of the articles quoted, which greatly enhances their value.

Clinical Endocrinology. By Karl E. Paschkis, M.D., Abraham E. Rakoff, M.D., and Abraham Cantarow, M.D. 2nd ed. (Pp. xii + 941; illustrated. £6 15s.) London, etc.: Cassell & Co. Ltd. 1958.

This is the second edition of a book which was very well received when it first appeared. It is written by an endocrinologist with a considerable interest in physiology, an endocrinologist specializing in gynæcological work, and a biochemist. The combination should prove a strong one and indeed they do cover a wide field, but perhaps for this very reason some subjects are dealt with very much more successfully than others. In addition, books take so long to produce nowadays that, in a field which is expanding as rapidly as endocrinology, many parts may appear out of date by the time the book is published. For example, in Hashimoto's disease, no mention is made of autoimmunity, and concerning de Quervain's giant-cell thyroiditis there is no reference to the possibility of mumps as an ætiological factor. The section devoted to the ovaries, as might be expected, is extremely thorough and well documented. On the subject of hyperparathyroidism, however, no mention is made of the resistant and recurrent peptic ulcer which may be a feature of that condition. This book will be found to be a useful reference work by clinical endocrinologists.

Amid Masters of Twentieth Century Medicine. By Leonard G. Rowntree, M.D. (Pp. xviii+684; illustrated. 87s. 6d.). Springfield, Ill.: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1958.

Known in this country as the man who rescued James Parkinson from oblivion, Canadian-born Dr. Leonard G. Rowntree has had a distinguished as well as colourful career as teacher, clinician, research worker, and administrator in one of the most important periods of medical history. "Amid Masters of Twentieth Century Medicine: A Panorama of Persons and Pictures," while largely autobiographical, is at the same time the fascinating and authentic story of some of the greatest medical men and discoveries of his age. The book begins with the war on yellow fever and malaria (the author worked for a time with W. C. Gorgas); continues with Johns Hopkins Hospital, to which Dr. Rowntree was advised to go by Osler, with graduate training in European capitals; with his professorship at the University of Minnesota, his experiences in World War I, his period spent as Chief of Medicine at the Mayo Clinic and as Director of the Philadelphia Institution for Medical Research; and tells of some of his patients participating in the making of medical history, and of vacations at home and abroad. There are delightfully intimate accounts of such great figures as J. B. Murphy, Samuel Meltzer, "the man who made medical meetings interesting", Ehrlich, Sir James Mackenzie, Friedrich von Müller. The story of Banting's "miracle" is first class. The style of writing is pleasant and exudes what the author calls his *Lebensfreudigkeit*. The illustrations are copious, well selected, and beautifully reproduced, which probably accounts for the stiff price. Unfortunately the book is spoilt by careless proof-reading, e.g. Sir Robert Philips (throughout); Gutherie (p. xiii); Acquanimitas (p. xiv); W. G. Haskell for W. H. Gaskell (p. 157); Krumbhaer (p. 164); &c. The index is lengthy, but imperfect, e.g. there are 2 entries under Halsted, W. S., and 7 under Halsted, William S.

The Preservation of Eyesight. Edited by Sir Arthur Salusbury MacNalty, K.C.B., M.A., M.D.(Oxon.), F.R.C.P.(Lond.), F.R.C.S.(Eng.), D.P.H., Hon.F.R.S.(Edin.). (Pp. vi+107; illustrated. 12s. 6d.) Bristol: John Wright & Sons Ltd. 1958.

This book describes the structure of the eye and the ills to which it is subject in non-technical language with a view to interesting general practitioners, medical students, nurses, health visitors, health educators, school teachers, and others concerned with the prevention of disease and the maintenance of public health. Chapters are devoted to the structure and function of the eyes, their use and their nutrition. Defects of the eye form the subject of the next chapter including a section on myopia. The following chapters deal with common affections of the eye, diseases of the lens, retina, and optic nerve, temporary loss of sight and the eye in old age. Blindness and the prevention of diseases and injuries of the eye in industry each receive a chapter on their own. Eye testing and spectacles are described in brief, and the book closes with an account of the care of the eyes in general.

It is difficult for an ophthalmologist to be quite certain how much this book will convey to the man in the street. It attempts to condense the whole of ophthalmology within 100 pages and at the same time avoid technical terms as much as possible. The task is well-nigh impossible but this is a good attempt.

Oral Histopathology. By Martin A. Rushton, M.A., M.D., Odont.D., F.D.S. R.C.S.(Eng. & Edin.), and Brian E. D. Cooke, M.R.C.S., L.R.C.P., F.D.S. R.C.S.(Eng.). (Pp. viii+190; illustrated. 30s.) Edinburgh and London: E. & S. Livingstone Ltd. 1959.

The authors have described their book as an attempt "to show what is happening at a cellular level in the principal disorders of the teeth and neighbouring parts". This they accomplish by a very good series of photomicrographs which fill more than half of the 190 pages of this book, thereby reducing the text to a minimum.

The very strict subdivision of the contents of this book into four parts, namely (1) the teeth and their formative organs; (2) the periodontal tissues; (3) the oral mucosa; and (4) the mandible and maxilla, is perhaps an unhappy one, as the reader is forced to refer separately to each of these parts before completing his study of one particular lesion or entity, as, for example, cysts and neoplasms. This arrangement may also cause difficulty in integrating this book with the practical teaching of oral histopathology. Two of the most important oral diseases, dental caries and periodontal disease, are treated rather briefly. The inclusion of more low-power magnifications of these lesions would greatly aid the reader to orientate the existing illustrations and give a clearer understanding of the progressive nature of these conditions. The section on lesions of the oral mucous membrane is a very valuable and useful contribution to an undergraduate textbook.

The authors are to be congratulated in their presentation of oral pathology from a purely microscopical angle. Although the book is small it is very reasonably priced for the quality of printing and good reproduction of the photomicrographs.

Printed in England by Staples Printers Limited, at their Great Titchfield Street, London, establishment.